Future Health Assessment and Risk-Management Integration for Infectious Diseases and Biological Weapons for Deployed U.S. Forces

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ABSTRACT

The health of the United States armed forces has been viewed as a critical component of the strength, readiness, and effectiveness of the military's ability to meet various degrees of threats to peace, human rights abuses, and other global disasters in the United States and the world. Compared with any other country or entity in the world, the U.S. military has one of the best surveillance and monitoring systems for assessing the risk of infectious disease globally. The monitoring is broad-based, specific for a large list of pathogenic agents, but includes generic symptomology that might be due to a multitude of current, emerging, or reemerging microorganisms; the monitoring is also timely. Gastrointestinal illness and respiratory and skin infections remain a problem for deployed troops.

It is now well known that microbial infections can result in chronic outcomes associated with heart, neurological, and immunological disorders. Therefore, hospitalization data will no longer suffice as the sole measure of severity and lost effectiveness to the troop force at large. Better assessment of antibiotic-resistant bacteria, coxsackieviruses, and Legionella and an evaluation of the underdiagnosis and underreporting of protozoa such as Cryptosporidium are needed. New microorganisms are being reported every year that might be associated with many of these illnesses, and prospective surveillance might be needed using new techniques to better understand the infection rates and asymptomatic infections.

Risk-assessment methods can now be used to quantify the risk of microbial infections and to address exposure and potential outcome from naturally occurring microorganisms and biological weapons. Hazard identification includes the identification of the microbial agent as well as the spectrum of human illnesses ranging from asymptomatic infections to death. The host response to the microorganisms with regard to immunity and multiple exposures should be addressed here, as well as the adequacy of animal models for studying human impacts. Endemic and epidemic disease investigations, case studies, hospi-

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talization studies, and other epidemiological data are needed to complete this step in the risk assessment. The variables need to be carefully defined and the data quantified as ratios. The dose-response assessment is the mathematical characterization of the relationship between the dose administered and the probability of infection or disease in the exposed population. Dose-response assessments have been referred to as probability-of-infection models, which are developed from mostly human volunteer studies. The exposure assessment determines the size and nature of the population exposed, the route, concentrations, and distribution of the microorganisms, and the duration of the exposure. The description of exposure includes not only occurrence based on concentrations but also the prevalence (how often the microorganisms are found) and distribution of microorganisms in space and over time. Exposure assessment is determined through occurrence monitoring and predictive microbiology. Quantitative risk characterization should estimate the magnitude of the public health problem, and demonstrate the variability and uncertainty of the hazard, using four distributions: (1) the spectrum of health outcomes; (2) the confidence limits surrounding the dose-response model; (3) the distribution of the occurrence of the microorganism; and (4) the exposure distribution. Assessments of occurrence and exposure can be further delineated by distributions surrounding the method of recovery and survival (treatment) distributions.

The risk-assessment framework already fits into the Department of Defense's (DOD's) programs associated with risk management. The critical need will be the development of databases that can be used in the decision and management process. Although health outcomes and morbidity and mortality statistics are available from numerous databases and surveillance programs, the data lacking are often the long-term assessments and chronic outcomes. The exposure assessment, particularly during deployment, is more suspect to uncertainty, especially in terms of quantitative evaluations. Geographic, climatic, seasonal, dose-response, and exposure scenarios can be used to develop tools for setting priorities for assessment of predeployment risks. Risk models can be evaluated for plausibility during outbreak investigations or disease surveillance operations. Exposure and health outcomes must be better assessed.

The use of quantitative assessments allows one to begin to build exposure scenarios in which thresholds associated with ineffectiveness in the troops in a given time frame can be determined for specific agents. For biological weapons, dose-response models should be developed and time and concentration exposure and consequence scenarios should be built and evaluated.

Finally, the formal expansion of DOD's mission on emerging infectious diseases in June 1996 by Presidential Decision Directive NSTC-7 now includes global surveillance, training, research, and response. One of the major assets in implementing this new directive is the overseas research laboratory system that is currently in place: the DOD Infectious Disease Research Laboratories. At a minimum, each laboratory staff should be trained in risk-assessment methods, should have molecular capabilities (polymerase chain reaction [PCR]), and be trained in the use of the global information system (GIS) for maintaining and analyzing the databases.

INTRODUCTION

The health of United States armed forces has been viewed as a critical component of the strength, readiness, and effectiveness of the military's ability to meet various degrees of threats to peace, human rights abuses, and other global disasters in the United States and the world. Much effort has gone into the development of frameworks for addressing the hazards that the military might face, particularly when deployed to hostile and foreign environments. A deployment of U.S. troops is defined as a "movement resulting from a Joint Chiefs of Staff /unified command deployment order for 30 continuous

days or greater to a land-based location outside the United States that does not have a permanent U.S. military medical treatment facility" (Memorandum for Under Secretary of Defense for Personnel and Readiness, Office of the Chairman, The Joint Chiefs of Staff, December 4, 1998).

There has been a tremendous change throughout the twentieth century in the types of health risks that the armed forces might face, and in the ability to identify and monitor these risks and to manage or control them. Health surveillance has improved and there is an enhanced ability to monitor the environment for hazardous exposures. Despite these gains, as the twenty-first century nears, the world is faced with the emergence and reemergence of infectious diseases. Disease surveillance at the global level has identified, in addition to endemic levels of diarrhea and respiratory disease, new bacteria, parasites, and viruses. These have been identified through dramatic outbreaks such as Legionnaire's disease from the bacterium *Legionella* and hemorrhagic fevers associated with the Hanta virus and other types of viruses; specific studies associating peptic ulcer disease and *Helicobacter*; epidemic levels of bloodborne and sexually transmitted HIV; and outbreaks of *Cryptosporidiosis* from drinking water and *Escherichia coli* 0157:H7 from food (Lederberg 1997). In addition, antibiotic resistance has emerged, causing a threat to the control of old-world killers such as tuberculosis.

There is currently a greater appreciation of the diversity, adaptability, and evolutionary complexities associated with infectious diseases, and much of this appreciation has been gained through research and studies with new molecular techniques. The technological advances in the study of microbiology, infectious disease, and molecular biology have also paved the way for a potential increased risk associated with the development and use of biological weapons.

Force Health Protection (FHP) is a framework that describes procedures for assessing the types of hazards, the exposure and populations at risk, and the monitoring of the health of all personnel deployed. FHP and other force protection plans have adapted various versions of the National Research Council's (NRC's) risk-assessment paradigm and integrated this assessment into management strategies to address the health of troops before, during, and after deployment and to protect defense personnel from hazardous chemicals and toxic materials. The use of this type of framework for biological and infectious agents is relatively new.

Risk-assessment methods following the NRC paradigm were initially used on a limited scale for judging waterborne pathogenic microorganisms (Haas 1983; Gerba and Haas 1988; Regli et al. 1991; Rose and Gerba, 1991; Rose et al. 1991; Haas et al. 1993). Haas (1983) was the first to look quantitatively at microbial risks associated with drinking water based on dose-response modeling. Rose et al. (1991) used an exponential model with quantitative risk assessment in the development of the Surface Water Treatment Rule to address in particular the performance-based standards for the control of *Giardia* as part of the requirements under the Safe Drinking Water Act (EPA 1989). Currently, risk assessment is being used for assessing food protection programs.

In a study for the U.S. Army, Cooper et al. (1986) attempted to quantify the risks of water-related infection and illness to Army units in the field. They reviewed the literature on infectious dose and clinical illness for potential waterborne pathogens. Using this information, the probability of infection was assessed using logistic, beta, exponential, and lognormal models. A generalized model was then developed incorporating expected pathogenic concentrations, consumption volume, and risk of infection for different military units. The study attempted to incorporate organism concentrations, effective treatment, and risk of infection. This attempt, however, was hampered by a limited existing database on microbial concentrations and infectious dose.

Quantitative microbial risk assessment (QMRA) has now gained wide acceptance in the evaluation of waterborne and foodborne disease. Methods and databases for development of QMRA for microbial agents associated with airborne, vectorborne, and dermal exposure have received less attention. How-

ever, the data on health, exposure, and dose-response, although limited, might be sufficient for undertaking preliminary risk assessments. The development of QMRAs along with improved methods for environmental monitoring will likely lead to more effective management and prevention strategies for U.S. deployed troops.

The purpose of this report is to:

- summarize the emerging infectious diseases and microbiological contaminant risks that U.S. deployed troops might face currently and in the future;
- briefly examine the various health disease databases that are available; and
- address quantitative research and data needs for integration of the microbial and biological risks into DOD risk-assessment and risk-management frameworks.

REVIEW OF PAST INCIDENCES AND FUTURE RISKS

Disease and Non-Battle-Injury Reports

Health promotion and disease prevention in the field are seen as critical to deployed troops, because illness can significantly compromise the objectives of the mission. Surveillance of infectious disease risks are determined by measured rates, usually as the number of people who have disease X per 1,000 or 10,000 people per some unit of time. In U.S. health databases, the rates are usually reported on an annual basis per 10,000 or 100,000 people. It is important to understand that most infections and diseases are underreported because of the failure of individuals to seek medical attention, laboratories to conduct proper tests, and the reporting system.

The identification of disease (or illness) is made by one of several methods (Table 1). The difference between disease and illness is minor in some cases. Disease is defined as the process or mechanism that ultimately results in an illness or a condition that impairs vital functions. An individual could have a disease without initially having any symptoms. Symptoms are effects of the illness that can be described by the individual who is ill, also known as self-reporting (e.g., headache, diarrhea, stomach cramps, vomiting, fatigue). Clinical assessment of the illness is generally defined by a measurable description of the illness (e.g., fever, bloody stool). Infection is colonization of the microorganism in the body and might result in disease and symptoms, which is the initial step in the microbial disease process. However, this can also result in asymptomatic, or subclinical, infections. Symptoms and clinical descriptions (fever, rash, inflammation) can be very specific, as with measles, which is associated with one specific agent, or they can be generic, as with diarrhea, which is associated with many different types of microorganisms.

The second means of identification is clinical diagnosis, which is the detection of the specific microorganism in a host specimen (e.g., laboratory identification in a liquid stool of an enteric pathogen). This requires the collection of a specimen (sputum, feces, blood, biopsy) and a specific diagnostic test (specific growth, biochemical tests, stains, genetic or protein markers, microscopic identification). This also means that there is some understanding of the agents that might be responsible for the disease symptoms and the process of disease resulting in the infection of specific cells or organs in the body. Infection without the individual reporting symptoms (an asymptomatic infection) can be detected by clinical diagnosis.

The final method of identification is associated with the response of the host system to infection that elicits an antibody response that can be detected in blood or, in some cases, saliva. This antibody response might be associated with past or current exposure, and in some cases, depending on the type of antibody and amount, one can determine the approximate timing of the exposure and infection. Expo-

TABLE 1 Methods for Diagnosing Infections and Disease

Method	Approach	Advantages and Disadvantages
Symptoms and clinical descriptors	Based on individual's feelings (headache) and measurable impacts (fever, rash).	Can easily diagnose, or identify individuals; however is not generally agent specific but more generic (e.g., diarrhea).
Clinical diagnosis	Based on testing specimens (sputum, feces or blood) for presence of the agent.[a]	Can specifically identify agent; however individual must deliver a specimen and there must exist a test method for the agent.
Antibody response (serological testing)	An indirect test (blood or in some cases saliva) for the presence of antibodies that the body produces as a result of infection.[b]	Is specific to the agent and in some cases might be able to determine the timing of the exposure and infection. Test method must exist.

[a]Asymptomatic infections can be detected.
[b]Antibody response may or may not be protective from subsequent exposure and infection and does not usually occur without infection.
Source: Haas et al. 1999.

sure without infection rarely causes an antibody response, except in the case of repeated exposure to very high concentrations of the agent, such as occurs with some vaccinations.

The Disease and Non-Battle-Injury (DNBI) reporting system is a tool used at the unit level to assess the "vital signs of the unit." This system is set up to evaluate the health of individuals predeployment, during deployment, and post-deployment. The primary function of the DNBI reports is to bring immediate attention to unacceptable high rates of illness, and thus to provide better prevention, treatment, and intervention in a timely manner.

During predeployment, health is evaluated on self-reporting of symptoms; only a few specific tests are undertaken. Blood samples were rarely collected until the Bosnia deployment. Readiness is addressed through education and management approaches and immunizations:

- Health assessment undertaken based on self-reporting of symptomology. Testing for specific type of microbial agent only with referral.
- Specific tests: HIV (within 12 months) and tuberculosis skin test (within 24 months).
- Education on known biological, chemical, and physical hazards (providing known countermeasures, e.g., insect repellant).
- Immunizations: Required are tetanus-diphtheria, influenza, hepatitis A virus (HAV), measles-rubella/measles-mumps-rubella (MR/MMR), and polio. Others might include yellow fever, hepatitis B virus (HBV), typhoid, and plague.

During deployment, the DNBI reports are made weekly. The tracking of disease is summarized weekly and reported at measured rates in percentages based on the number of patients seen divided by the average troop strength deployed. These reports are based on self-reporting illnesses of a serious enough level to require a visit to the medical staff. Primary complaints and final diagnoses are included in the report, as well as days of light duty, lost work days, and admissions. Text Box 1, from the Memorandum for Under Secretary of Defense for Personnel and Readiness, Office of the Chairman, The Joint Chiefs of Staff, December 4, 1998, has the list of infectious agents that are reportable.

TEXT BOX 1
Tri-Service Reportable Medical Event List

- Amebiasis
- Anthrax
- Biological Warfare Agent Exposure
- Botulism
- Brucellosis
- Campylobacter
- Carbon Monoxide Poisoning
- Chemical Agent Exposure
- Chlamydia
- Cholera
- Coccidioidomycosis
- Cold Weather Injury (All)
  - Frostbite
  - Hypothermia
  - Immersion Type
  - Unspecified
- Cryptosporidiosis
- Cyclospora
- Dengue Fever
- Diptheria
- E.coli 0157:h7
- Ehrlichiosis
- Encephalitis
- Filariasis
- Glardiasis
- Gonorrhea
- H. Influenzae, Invasive
- Hantavirus Infection
- Heat Injuries
  - Heat Exhaustion
  - Heat Stroke
- Hemorrhagic Fever
- Hepatitis A
- Hepatitis B
- Hepatitis C
- Influenza
- Lead Poisoning
- Legionellosis
- Leishmaniasis (All)
- Leishmaniasis.
  - Cutaneous Leishmaniasis.
  - Mucocutaneous Leishmaniasis.
  - Unspecified Leishmaniasis. Visceral
- Leprosy
- Leptospirosis
- Listeriosis
- Lyme Disease
- Malaria (All)
  - Malaria. Falciparum
  - Malaria. Mmalariae
  - Malaria. Ovale
  - Malaria. Unspecified
  - Malaria. Vivax
- Measles
- Meningococcal Disease
  - Meningitis
  - Septicemia
- Mumps
- Pertussis
- Plague
- Pneumococcal Pneumonia
- Poliomyelitis
- Q Fever
- Rabies, Human
- Relapsing Fever
- Rheumatic Fever, Acute
- Rift Valley Fever
- Rocky Mountain Spotted Fever
- Rubella
- Salmonellosis
- Schistosomiasis
- Shigellosis
- Smallpox
- Streptococcus. Group A, Invasive
- Syphilis (All)
  - Syphilis. Congenital
  - Syphilis. Latent
  - Syphilis. Primary/ secondary
  - Syphilis. Tertiary
- Tetanus
- Toxic Shock Syndrome
- Trichinosis
- Trypanosomiasis
- Tuberculosis. Pulmonary
- Tularemia
- Typhoid Fever
- Typhus Fever
- Urethritis. Non-gonococcal
- Vaccine, Adverse Event
- Varicella, Active Duty Only
- Yellow Fever

Source: Memorandum (MCM-251-98) from Chairman of the Joint Chiefs of Staff dated 04 December 1998.

Suggested reference rates are rough general guidance numbers (acceptable limits); rates above these rates might indicate a problem. Expert judgment is used to make final decisions regarding the immediacy of the risks and the actions to be taken in further assessment and control. Temporal trends of illness are also tracked. Table 2 shows suggested limits for categories of general illnesses.

Upon post-deployment, health evaluations are again made by self-reporting of symptoms. Positive responses are followed up. However, no testing is undertaken routinely.

It is generally accepted that surveillance systems greatly underestimate the level of disease in any given community and, although providing a picture of past risk, thus might not accurately reflect future risk. This becomes problematic for emerging pathogens for which there is no established procedure for testing patients, and surveillance systems rarely address the various exposure or transmission pathways.

TABLE 2 Weekly DNBI Report for Category of Illness and Suggested Acceptable Levels

Category	Suggested Reference Rate[a]
Combat/operational-stress reactions	0.1% (1/1,000)
Dermatological	0.5% (5/1,000)
GI, infectious	0.5%
Gynecologic	0.5%
Heat/cold injuries	0.5%
Injury: recreational/sports	1.0% (10/1,000)
Injury: motor vehicle accidents	1.0%
Injury: work/training	1.0%
Injury: other	1.0%
Ophthalmologic	0.1%
Psychiatric, mental disorders	0.1%
Respiratory	0.4% (4/1,000)
STDs	0.5%
Fever, unexplained	0.0%
All other medical and surgical	
Total DNBI	4.0% (40/1,000)

[a]Time frame is weekly assessment.

Source: Memorandum (MCM-251-98) from Chairman of the Joint Chiefs of Staff dated 04 December 1998.

TABLE 3 Advantages and Limitations of the DNBI Report

Advantages	Limitations
1 Reports on generic symptoms (GI, respiratory).	1. Excludes *Helicobacter* and most enteric viruses.
2. Large number of agents that are reportable (Textbox 1).	2. Relies primarily on self-reporting; clinical diagnosis might not be routine (e.g., are all diarrhea specimens examined for *Cryptosporidium*?) and antibody assessments (seroprevalence data) are not routinely included (only in specialized reports).
3. Weekly reporting.	3. Report is indication of past exposures and might not indicate the route of exposure.
4. Severity data recorded (days lost, hospitalization).	4. Data on the unknown etiologies category are not included in the sum total.

In addition, outcome might be assessed by mortality in the extreme case or without identification of consequence (e.g., severity of the illness, number of days sick, medical care).

The advantages of the DNBI reporting system over most systems are in the broad scope of the specific and generic assessments made and the timeliness of the reporting. The DNBI systems might then identify unknown pathogens or microorganisms that cause more than one type of symptom in those exposed. There are a few limitations; for example, ulcers from the gastrointestinal infections are excluded, although it is now recognized that *Helicobacter* is a cause of this type of illness (Taylor and Blaser 1991). In addition, because most illnesses are exhibited after an incubation time ranging from 1 day (bacteria), 7 days (parasite), to 21 days (HAV), the DNBI record is a record of past exposures (Table 3).

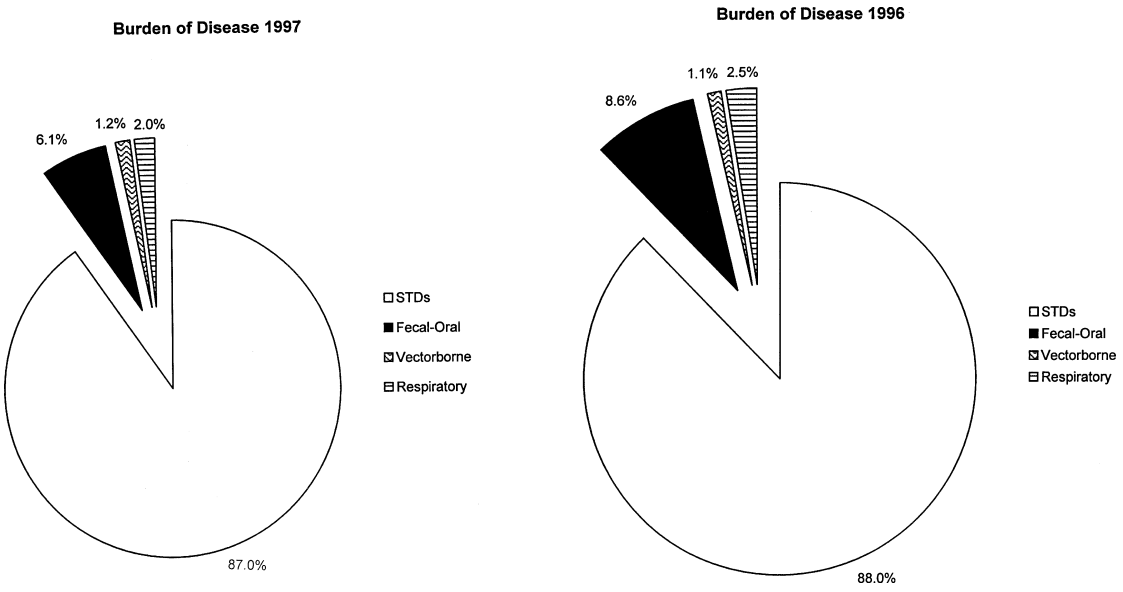


FIGURE 1 Conditions reported by the Defense Medical Surveillance System, Jan.-Dec., 1996 and 1997 (MSMR 1997a, 1998a).

The Defense Medical Surveillance System reports all DNBI data on a monthly basis. The following is a brief review of the cumulative 1997 and 1998 reports, followed by some summaries and conclusions.

Figure 1 shows the disease reports for 1996 and 1997 within the military for four main categories of illnesses by route of transmission (sexually-transmitted disease [STD], fecal-oral, vectorborne, and respiratory). These data come from 7,061 case reports in 1996 and 10,007 case reports in 1997. STDs accounted for 88% and 87% of the cases in 1996 and 1997, respectively (chlamydia, gonorrhea, urethritis, herpes, and then syphilis). Fecal-oral agents were second, contributing to 8.6% and 6.1% of the cases for the two years, respectively. Included in the top four in descending order were *Salmonella*, *Campylobacter, Shigella,* and *Giardia* in 1996, and *Salmonella*, *Shigella, Campylobacter,* and *Giardia* in 1997. Guillain-Barré syndrome, a neurological complication associated with *Campylobacter* infections was reported in both years (3 and 4 cases, respectively). This outcome has also been related to reactions to immunizations (Medical Surveillance Monthly Report (MSMR) 1995). Viral meningitis could likely be due to enteric viruses and should be considered fecal-oral (41 and 92 cases, respectively). Respiratory illness contributed to 2.5% and 2.0% in 1996 and 1997, respectively, with varicella contributing to most other cases, followed by influenza and tuberculosis. Vectorborne diseases were associated with 1.1% and 1.2% of the cases for 1996 and 1997, respectively. Malaria, leishmaniasis, and Lyme disease were the top microbial pathogens in this category.

Hospitalization records and days lost from effective work were used to evaluate the severity of the outcomes. When muscular and joint problems were excluded (which are the number one cause of reported hospitalizations) the top five causes of hospitalizations were diseases of the digestive system, followed by respiratory diseases, genitourinary diseases, infectious and parasitic diseases, and diseases of the skin and subcutaneous tissue (Figure 2).

These data are for all troops stationed in the United States, Europe, Pacific, and other regions (e.g., Korea). No discernable differences were noted geographically for the STDs. Although STDs are

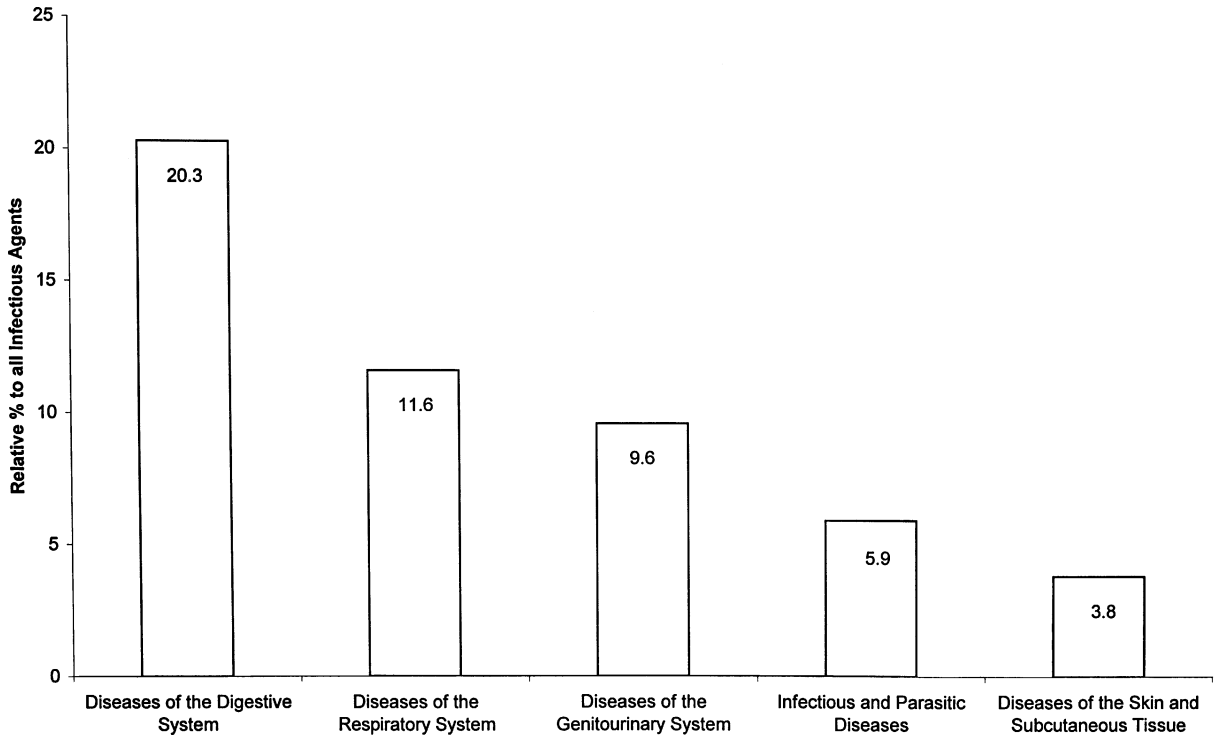


FIGURE 2 Severity based on active-duty hospitalization rates, U. S. Army (MSMR 1998b).

problematic, the attendance by a physician, diagnosis, and reporting are likely much greater than many of the other types of infections; thus, the infectious disease risks based on this reporting system appear skewed. These data might be particularly misleading regarding the risk for deployed troops outside the United States. The completeness of reporting is dependent on the etiological agent; for example, for the two militarily important tropical infectious diseases, malaria and leishmaniasis, reporting was 67% and 81% complete. Reporting of varicella and Lyme disease was 20 to 25% complete. For diseases such as hepatitis, dengue, and campylobacteriosis, 0% were reported of those that were reportable. Therefore, underreporting is likely a problem for many of the fecal-oral and respiratory agents.

Respiratory disease is one that continues to plague the troops. Recruits, trainees, and those upon initial deployment appear to be at greater risk. Immunizations are available for adenovirus Type 4 and Type 7 and the influenza viruses (Table 4). However, outbreaks of influenza continue to occur due to the variety of subtypes that exist throughout the world. In an outbreak of influenzalike illness in an aviation squadron in Hawaii, the efficacy of the vaccine for preventing the illness was only 16.7% (MSMR 1998c). Therefore, use of year-round vaccination and treatment has been able to reduce the respiratory disease but has not been able to eliminate it.

The military's surveillance program for respiratory disease includes 14 sentinel bases (seven foreign bases, Germany, Guam, two in Japan, Korea, Turkey, and United Kingdom, and seven U.S. bases, Alaska, California, Colorado, Mississippi, New Jersey, and two in Texas). Throat swabs are obtained from those who meet a case definition; therefore, asymptomatic cases are not detected.

Transmission of respiratory agents can be person to person through hands (thus handwashing can facilitate prevention) or through contaminated fomites (surface disinfection might prove useful for

TABLE 4 Results of the 1995-1996 Respiratory Surveillance Program

Microorganism	Number Isolated	Treatment/Vaccine	Comments
Streptococcus A	86/1,071	Benazthine	
Beta hemolytic	8%	Penicillin	
		Chemoprophylaxis	
Total viruses	512/1,634		
	31.8%		
Influenza A	358/1,634	Vaccines	Nov. -Jan. peak
	22%		
Influenza B	56/1,634	Vaccines	Mar. -May peak
	3.4%		
Enteroviruses	~52	None	
	3.2%		
Adenoviruses	~27	Vaccine for Types 4 and 7	
	1.6%		
Parainfluenza	~12	None	
Types 1, 2, and 3	0.7%		
Herpes simplex virus	~8	None	
	0.5%		

Source: MSMR 1996a.

prevention), and enteroviruses (coxsackieviruses) might account for some of the dramatic spread of infections through troops. Respiratory transmission (aerosolization) is the final route, although in some cases the pathway is not very well defined. Interestingly for Group A streptococci, Ferrieri et al. (1972) have proposed a sequence of spread from skin infections to the nose and throat (Figure 3). This bacterium is one of the major causes of impetigo and has been associated with infections after scratches and bites from insects, which can be controlled to some extent through the use of antibacterial lotions applied to the abrasions. The seasonality of diseases such as influenza has been hypothesized to be a result of animal reservoirs and survival potential of the pathogenic agent.

For those on active duty, coming from field sites, Adult Respiratory Distress Syndrome (ARDS) apparently is common. Studies have reported on individual cases of ARDS (MSMR 1997b); however, the etiologies, trends, and rates have not been reported, although studies are under way. Therefore, unknown respiratory illnesses are likely the majority of the reported cases of ARDS.

Fever of unknown origin (FUO) is a term described for those experiencing elevated temperature that could not be ascribed to any specific agent. Studies on the more severe cases (those hospitalized for 1 day or more) reported a rate of 2.68/100,000 (0.03/1,000) per month. Of these cases, 45% were diagnosed upon primary assessment as FUOs and in 12.7% that was the only diagnosis (total of 1,437 hospitalizations from 1990-1997 (MSMR 1998d). Vaccine reactions were found to be contributing to 5.3% of these FUOs, and other types of unknown infections, throat (7.4%), respiratory (2.1%), and gastrointestinal (4.9%), accounted for much of the remainder. Infantry men more than any other military occupational group were found to be at a greater risk among those hospitalized three days or longer where vaccine reactions were eliminated. The diagnosis and reporting of FUOs has been inconsistent for those FUOs of shorter duration (1 to 2 days); trends and unusual occurrences are more difficult to ascertain due to the high variability. The more severe illness, which lasts for more than 3 days, shows much less variability.

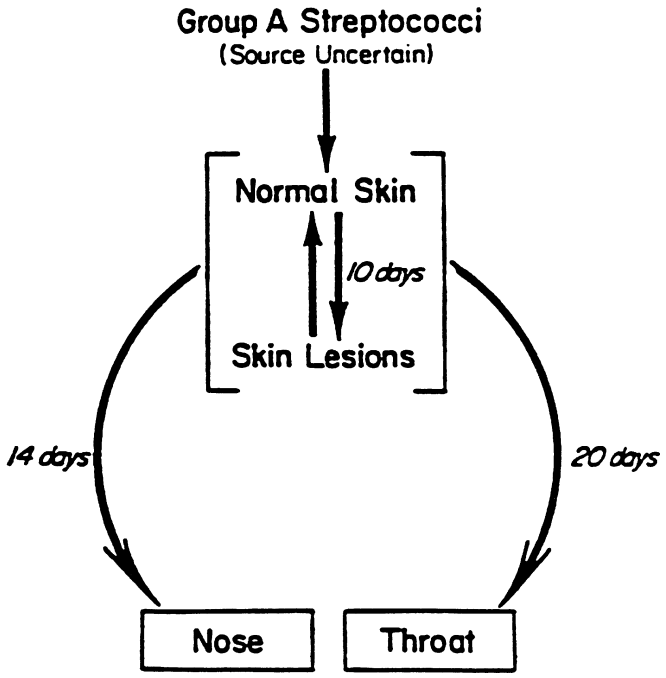


FIGURE 3 Concept of the sequence of spread of Group A streptococci among different body sites (Ferrieri et al. 1972).

Reports on deployment surveillance have shown that gastrointestinal and respiratory risks are the most significant cause of immediate acute outcomes associated with clinic visits and hospitalizations. Trends also demonstrate a decrease in the number of cases with time. Therefore, the greatest burden of illness is reported early on in deployment.

Gastrointestinal illness was the leading cause of morbidity among U.S. troops in the Persian Gulf deployment during 1990-1991 (Hyams et al. 1995). Parasitic infections were not found to be a significant cause of disease. Although *Escherichia coli* and *Shigella sonnei* were the primary pathogens identified, of great concern was the high level of antibiotic resistance identified (20 to 80% of the isolates were resistant). Outbreaks of the Norwalk virus and other unknown etiologies likely to be viruses were common. Serological investigations (antibody testing) found 6% of the combat units might have been infected with the Norwalk virus. The source of the diseases was associated primarily with vegetables and fruits imported from neighboring countries. It is clear from the identification of the *Shigella* and Norwalk agents that human fecal wastes and perhaps untreated sewage were the cause of much of the contamination.

Diarrheal disease was also quite high in an exercise in Thailand, and risks there were also associated with consumption of indigenous foods (MSMR 1998e). Gastrointestinal outbreaks have been associated with both food and water. A United Nations deployment to Haiti in June 1995 experienced a suspected waterborne outbreak due to the consumption of unapproved bottled water. The rate ranged between 15 to as high as 94 cases per 1,000 per month, with a high weekly rate seen in the third month (40/1,000/wk).

Common cold and upper respiratory complaints were common during deployment. Studies found that troops living and working in tightly constructed air conditioned buildings were at greatest risk. Possible causes of this, such as *Legionella*, were not investigated.

Comparing hospitalizations with clinic visits demonstrates that the level of disease in a force is likely to be 50 to 100 times greater than what is reported by hospitalization rates. This has been shown

TABLE 5 Examples of DNBI and Hospitalization Rates Associated With Deployments

	GI	Respiratory	Time Frame
Bosnia hospitalization trends	8.76/1,000	2.85/1,000	Cumulative incidence (48 weeks)
Gulf War outpatient visits	1 to 39/1,000[a]	1 to 22/1,000[b]	Range of weekly rates of outpatients in 40,000 troops (31 weeks)
Thailand clinic visits	12/1,000	9/1,000	Average visits per week

[a]Highest rates seen in the fourth to fifth week associated with fresh fruits and vegetables.
[b]Highest rates seen in the first two weeks and a second peak seen during U.S. Marine Expeditionary Forces deployment.
Sources: Hyams et al. 1995; MSMR 1997c, 1998e.

in numerous outbreaks where hospitalizations and case data were compiled (see following section on building databases). Although mild diarrhea might not affect the individual's activities to any great extent, it is more than likely that 1 to 3 days of effective time were lost. Table 5 shows some examples of DNBI and hospitalization rates associated with deployments (Hyams et al. 1995; MSMR 1997c; MSMR 1998e). Notice that the rates during the Bosnian deployment for the severe cases are reported over the complete time frame, whereas the rates for the Persian Gulf and Thailand deployments are reported for a range and an average of weekly clinic visits. It is most appropriate to report both visits and hospitalizations for comparisons over the time of the deployment. The disease levels from one deployment to another need to be examined in light of exposure tied to sources, season, and geographic locale, as well as changes in policies that factor in decreasing the risks.

Vectorborne diseases have also been shown to emerge during deployment. During Operation Desert Shield/Storm in eastern Saudi Arabia, 12 cases of viscerotropic and 20 cases of cutaneous leishmaniasis were identified (697,000 allied soldiers deployed; cumulative rate of 0.017/1,000 and 0.03/1,000 cases, respectively; 4.3/1,000 cases of cutaneous leishmaniasis seen in the Colombian Army) (Martin et al. 1998). The parasite is transmitted through bites from the sand fly. Domesticated animals can serve as reservoirs, and in Italy two cases of this disease in children of active-duty members might have been due to the high prevalence of the disease (15-50%) in dogs (MSMR 1998f). Attack rates of the disease in other deployments have been as high as 60%, with exposures of only 6 hours.

Physical protection, such as using nets, DEET lotion, and treating bedding and clothing, is seen as paramount to control. Education and predeployment training as well as better entomological surveillance will provide better preparedness. Clearly one of the lessons learned during Operation Desert Storm was that previous reports on the geographic areas at risk had missed this part of Saudi Arabia. In addition, chronic effects that might be exhibited post-deployment as a result of such exposures will need to be considered.

A combined U.S.-Australian military operation in Queensland, Australia, in March 1997 exhibited the successful approach that is used by the military for control of vectorborne diseases (MSMR 1997d). Arboviruses were endemic to the region and the exercise corresponded to the seasonal peak of transmission of the Ross River virus (RRv). Entomological surveys found RRv in four mosquito species. Out of the 9,000 troops who were engaged in ground operations, six cases of the disease were confirmed through serological testing and clinical manifestations (0.67/1,000 cases). The use of personal measures that protect against the mosquito were reinforced, and in fact it was found that protective measures were not adhered to by those who became ill.

Twelve cases of malaria associated with those who had served in Korea were reported, and seven cases of leptospirosis, all in children, were reported in the Pacific region (MSMR 1997e; MSMR 1996b; MSMR 1998g). Malaria is caused by a mosquitoborne protozoan and leptosporosis is spread through contact with water contaminated with urine from infected animals.

Emerging Infectious Agents

Worldwide, the leading cause of death remains the variety of infectious diseases that plague human beings. In the United States, the risk of dying from an infectious disease rose from fifth place to third place just in the last decade due to emerging and reemerging microorganisms. It is also clear that acute end points of disease are inadequate to describe the risks, and many chronic diseases, heart disease, neurological disorders, and cancer are due to microbial infections (Table 6). New microorganisms are identified each year and well-recognized pathogens have reemerged (Figure 4). Health outcomes and the ability to diagnose diseases as well as the potential for exposure will ultimately influence the assessment of these microbial agents.

Fecal-Oral Agents

Fecal-oral agents can be transmitted through person to person contact and contaminated water and food, as well as through surface contact. Zoonotic potential is a critical issue and in some cases transmission through the food chain, such as *Salmonella enteritis* in eggs, needs to be identified as the key risk. Microorganisms are excreted in feces in high numbers, survive in the environment, are resistant to many conventional treatment processes, and cause infections at low exposure levels. Given that most of the world fails to treat human and animal wastes prior to discharge in water, the risk of exposure remains significant.

Enteric Viruses

There are several hundred enteric viruses that have been identified and new types are being reported. Some of the key concerns with these viruses includes issues regarding health outcome and exposure assessment include:

- New viruses are being discovered (picobirnaviruses).
- Chronic health outcomes are now known.
- Groundwater contamination and potential exposure is high.
- Survival during cooking has been documented (e.g., shellfish).

Hepatitis A virus is considered to be endemic in most Latin American and Caribbean countries (Craun 1996). Although the risk of exposure is high, there is a vaccine available. The symptoms of hepatitis A include fever, nausea, anorexia, and malaise, often with mild diarrhea. The liver cells are ultimately infected causing cytologic damage, necrosis, and inflammation of the liver. Illness usually lasts from 1 to 2 weeks but might last several months. A new and emerging concern worldwide is other types of viral hepatitis.

Devastating waterborne disease outbreaks of the hepatitis E virus (HEV) have occurred in some parts of the world but not in others. In Kanpur, India, in 1991, there were 79,000 cases of HEV due to sewage contamination of the drinking water. Children are often asymptomatic and the mortality rate is between 0.1 and 4% (Grabow et al. 1994). In pregnant women in their third trimester, the mortality rate

TABLE 6 Acute and Chronic Health Effects Associated With Various Microorganisms

Agent	Acute Effects	Chronic or Ultimate Effects
Bacteria		
E. coli O157:H7	Diarrhea	Adults: death (thrombocytopenia) Children: death (kidney failure)
Legionella pneumoniae	Fever, pneumonia	Elderly: death
Helicobacter pylori	Gastritis	Ulcers and stomach cancer
Vibrio vulnificus	Skin and tissue infection	
Campylobacter	Diarrhea	Death: Guillian-Barré Syndrome
Salmonella	Diarrhea	Reactive arthritis
Yersinia	Diarrhea	Reactive arthritis
Shigella	Diarrhea	Reactive arthritis
Cyanobacteria (blue-green algae) and other toxins	Diarrhea	Potential cancer
Leptospirosis	Fever, headache, chills, muscle aches, vomiting	Weil's Disease, death (not common)
Aeromonas hydrophila	Diarrhea	
Parasites		
Giardia lamblia	Diarrhea	Failure to thrive Severe hypothyroidism Lactose intolerance Chronic joint pain
Cryptosporidium	Diarrhea	Death in immunocompromised host
Toxoplasma gondii	Newborn syndrome Hearing and vision loss Mental retardation Diarrhea	Dementia and/or seizures
Acanthamoeba	Eye infections	
Microsporidia (Enterocytozoon and Septata)	Diarrhea	
Viruses		
Hepatitis viruses	Liver infection	Liver failure
Adenoviruses	Eye infections, diarrhea	
Caliciviruses (small round structured viruses, Norwalk virus)	Diarrhea	
Coxsackieviruses	Encephalitis Aseptic meningitis Diarrhea Respiratory disease	Heart disease (myocarditis), reactive insulin-dependent diabetes
Echoviruses	Aseptic meningitis	

Source: CDC 1997.

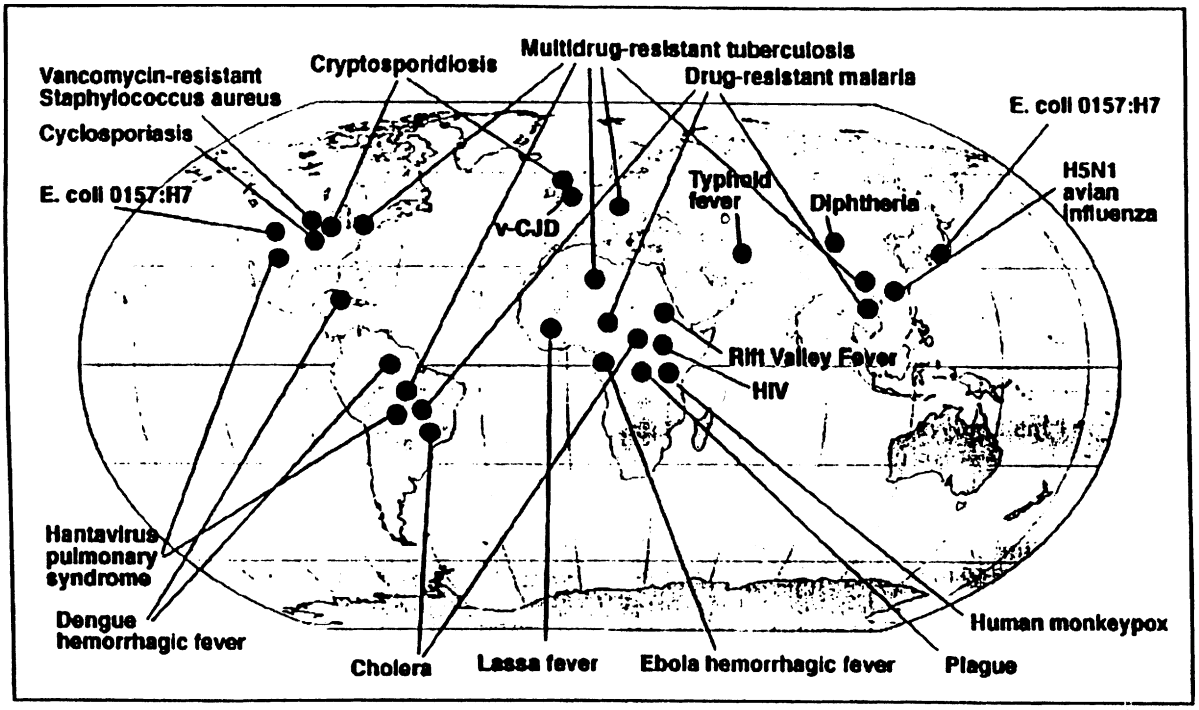


FIGURE 4 Examples of new and reemerging diseases (Fauci 1998).

can exceed 20% (Gust and Purcell 1987). There has been speculation HEV is endemic in various parts of the world, and subclinical cases might be contributing to the spread of the disease.

The coxsackieviruses now need to be considered separately as one of the enteroviruses that might be related to more significant risks (Bendinelli and Friedman 1988).

Diarrhea has been one of the risks associated with many of the enteric viruses such as Norwalk virus, but more serious chronic diseases have now been associated with viral infections and these risks need to be better defined. Studies have now reported that coxsackie B virus is associated with myocarditis (Klingel et al. 1992). In other recent studies, enteroviral RNA was detected in endomyocardial biopsies in 32% of patients with dilated cardiomyopathy and 33% of patients with clinical myocarditis (Kiode et al. 1992). In addition, there is emerging evidence that coxsackie B virus is also associated with insulin dependent diabetes, and infection with this virus might contribute to an increase of 0.0079% of these diabetes cases (0.079/1,000) (Wagenknecht et al. 1991).

Coxsackieviruses should be diagnosed serologically and clinically. Clinical conditions are associated with many systems including:

- Respiratory
- Central nervous system
- Cardiovascular
- Muscle and joints
- RE system and glands
- Gastrointestinal

Symptoms can include everything from general fatigue, headaches, and diarrhea to a fever.

Other concerns associated with coxsackieviruses are:

- Asymptomatic infections can lead to chronic outcomes (myocarditis).
- A multitude of symptoms can be seen in a population after exposure (heterogeneous outcomes).
- Coxsackie B viruses are commonly found in sewage.
- Concurrent exposure to the virus and other contaminants (e.g., metals) has demonstrated increased risk.

New viruses are continually being discovered and characterized, such as astroviruses, toroviruses, and small round structured viruses all associated with fecal-oral transmission and diarrhea. Although at one time the viruses were thought to be host-specific, the potential for zoonotic transmission from animals does exist. The picobirnaviruses (PBV) are unique double-stranded, bi- or tri-segmented RNA viruses, and are found in people and animals, including chickens (Chandra 1997). They have been shown to be a cause of acute diarrhea in children (Cascio et al. 1996) and prevalence in human stools was 9 to 13% with and without symptoms (Gallimore et al. 1995). Reports of PBVs have come from Italy; Caracas, Venezuela; and the United Kingdom, and it is likely that they have worldwide distribution.

Contamination of groundwater with viruses is of great concern due to the resistant nature of the viral structure and the colloidal size (20 to 80 nm), which makes this group of microorganisms easily transported through soil systems. Viruses also survive up to months in groundwater and are more resistant to water disinfection than are the coliforms (Yates and Yates 1988; Gerba and Rose 1990). Studies in the United States have found viruses in 20 to 30% of the groundwater where coliforms were not predictive of viral contamination (Abbaszadegan et al. 1999). New techniques using polymerase chain reaction (PCR) have shown that there is much more contamination than previously recognized (Table 7). There are no data on the occurrence of viruses in groundwater in most other parts of the world.

Protozoan Parasites

Cryptosporidium was first diagnosed in humans in 1976. Since that time, it has been well recognized as a cause of diarrheal illness (Dubey et al. 1990). Reported incidences of *Cryptosporidium* infections in human populations range from 0.6 to 20%, depending on the geographic locale. There is a greater prevalence in populations in Asia, Australia, Africa, and South America. *Cryptosporidium* is the most significant waterborne disease in the United States today. The occurrence of *Cryptosporidium* in surface waters has been reported in 4 to 100% of the samples examined at levels between 0.1 to 10,000/100 L, depending on the impact from sewage and animals (Lisle and Rose 1995). Groundwater, once thought to be a more protected source, has shown between 9.5 and 22% of samples positive for *Cryptosporidium* (Hancock 1998). In North America, there have been 12 waterborne outbreaks of *Cryptosporidium*. It has also been associated with drinking water outbreaks in the United Kingdom, Japan, and Holland. The largest outbreak in the United States occurred in Milwaukee, Wisconsin, in 1993 where 400,000 people became ill and 100 died due to contamination of the water supply (MacKenzie et al. 1994).

Cyclospora cayetanensis (previously called a cyanobacterium-like body) is a single-cell coccidian protozoan that has been implicated as an etiologic agent of prolonged watery diarrhea in humans (Ortega et al. 1993). The organism was first described as early at 1977 (Ashford 1979) and has been reported with increased frequency since the mid-1980s. *Cyclospora* has been described in patients from

TABLE 7 Virus Detection in Groundwater in the U.S. by Various Methods

Virus	Method	Percentage of Samples Positive
Culturable enteric viruses	Cell culture	6.8 (12/176)
Enteroviruses	PCR[a]	30
Hepatitis A virus	PCR	7
Rotavirus	PCR	13
Total viruses	PCR	39.3 (53/135)

[a]PCR, nucleic acid amplification for detection of the internal components of the virus, PCR may detect non-viable viruses.

Source: Abbaszadegan et al. 1999.

North, Central, and South America, Europe, Asia, and North Africa; however, the true prevalence of this parasite in any population is unknown (Soave and Johnson 1995).

Cyclospora is now known to be an obligate parasite of immunodeficient and immunocompetent humans (Ortega et al. 1993). In an immunocompromised person the parasite can cause profuse, watery diarrhea lasting several months. The infection is much less severe in immunocompetent patients. Symptoms can range from no symptoms to abdominal cramps, nausea, vomiting, and fever lasting from 3 to 25 days (Goodgame 1996).

Although *Cryptosporidium* appears to be predominantly waterborne, *Cyclospora* has been related more often to transmission through contaminated produce from a world market. The differences between the protozoa and their transmission might be due to their biology and structure, size of the oocysts, need for sporulation, and presence of animal reservoirs (Table 8).

Microsporidia are obligate intracellular spore-forming protozoa that are capable of infecting both vertebrate and invertebrate hosts. Their role as an emerging pathogen in immunosuppressed hosts is being increasingly recognized. The prevalence of microsporidiosis in studies of patients with chronic diarrhea ranges from 7 to 50% worldwide (Bryan 1995). It is unclear whether this broad range represents geographic variation, differences in diagnostic capabilities, or differences in risk factors for exposure to microsporidia. Typical symptoms of infection include chronic diarrhea, dehydration, and significant weight loss (>10% of body weight). Other symptoms include keratitis, conjunctivitis, hepatitis, peritonitis, myositis, central nervous system infection, and renal disease. Treatments are available for certain species of microsporidia; however, some species remain resistant to therapy.

In the United States there is currently a lack of data to suggest widespread occurrence of human strains of *Microsporidia* in surface waters. *Microsporidia* species that live in humans and animals have been detected in all water and wastewater (Dowd et al. 1998). However, because *Microsporidia* spores are excreted from infected individuals into wastewater, there is the potential for their occurrence in sewage contaminated waters. Animal hosts for *Microsporidia* also enhance the possibility that the organisms could be amplified and deposited into water supplies at high levels. *Microsporidia* spores have been shown to be stable in the environment and remain infective for days to weeks outside their hosts (Shadduck and Polley 1978; Waller 1979; Shadduck 1989). Because of their small size (1 to 5 μm), they might be difficult to remove using conventional filtration techniques, and there is a concern that these organisms might have an increased resistance to chlorine disinfection similar to *Cryptosporidium*.

Toxoplasma gondii is considered a tissue protozoan of cats and other felines that become infected mainly from eating infected rodents or birds, or from feces of infected cats. The disease has flu-like

TABLE 8 Comparison of *Cryptosporidium* and *Cyclospora*

Attribute	*Cryptosporidium*	*Cyclospora*
Taxonomy	Intestinal coccidian	Intestinal coccidian
Infective unit	Oocysts 4 –5 µm Immediately infectious upon excretion	Oocysts 8 – 10 µm Requires sporulation[a] in the environment, not immediately infectious upon excretion
Animal reservoir	*C. parvum* found in most mammals, can cross species barriers	*C. cayetanensis* documented only in humans
Foodborne disease	4 outbreaks in the U.S.	5 Large clusters in U.S. and Canada seen 1995, 1996, and 1997, involving >3,000 cases; primary transmission associated with fruits and vegetables
Waterborne disease	12 Waterborne outbreaks in North America since 1985, 17 in United Kingdom, 2 in Japan; primary transmission	1 Outbreak in Chicago, 1 in Nepal

[a]Sporulation is a process by which the oocysts undergo maturation in the environment before becoming infectious.
Source: Rose and Slifko, 1999.

symptoms, with swollen glands in the neck, armpits, or groin area. Most people recover without treatment. In the immunocompromised, the infection might cause severe disease, and infection during pregnancy might lead to fetal infection, chronic chorioretinitis, or death.

Foodborne transmission has been a source of toxoplasmosis; however, two outbreaks of the disease have been associated with contaminated surface water. In 1979, 600 U.S. soldiers attended a 3-wk training course in a jungle in Panama. Within 2 weeks of their return to the United States, 39 out of 98 soldiers in one company came down with a febrile illness. Serological testing revealed 31 confirmed cases of acute toxoplasmosis. The outbreak was attributed to the ingestion of contaminated water while on maneuvers in the jungle (Benenson et al. 1982).

In March 1995, the Capital Regional District of Victoria, British Columbia, identified 110 cases of toxoplasmosis. The outbreak was attributed to a single drinking water source for the area. The number of newly identified cases of toxoplasmosis declined sharply after the drinking water reservoir suspected of contamination was shut down. An estimated 3,000 people (1% of the population) might have been infected by the municipal drinking water contaminated with toxoplasmosis (Canadian Water Works Assoc. 1995).

Bacterial Pathogens

Epidemics of cholera have devastated Europe and North America since the early 1800s. A lack of sanitation and an increasing population, often with limited access to clean water, has brought about numerous disease outbreaks. A total of 1,076,372 cases and 10,098 deaths due to cholera in the Americas were reported by June 1995 according to the Pan American Health Organization (PAHO). In 1994, non 01 cholera was detected for the first time from the Bug River (freshwater) in Poland, and recently, Hong Kong has reported two outbreaks of cholera (Lee et al. 1996). Although the cause of the Hong Kong outbreaks was not clearly identified, increasing pollution of coastal waters has been implicated. Further concern over the cholera epidemic stems from the discovery of a new strain of *Vibrio cholera* 0139, which has resulted in increased mortality rate (Lee et al. 1996). Inadequate disinfection

or the lack of disinfection has contributed significantly to the spread of cholera throughout Africa and Latin America. Water, seafood, and rice are common vehicles for spreading the disease.

Helicobacter pylori has been cited as a major etiologic agent for gastritis and has been implicated in the pathogenesis of peptic and duodenal ulcer disease (Taylor and Blaser 1991). It has also been associated with the development of gastric carcinoma (Eurogast Study Group 1993). The mode of transmission of *H. pylori* is not well characterized. Recent studies suggest that some gastrointestinal dissemination might be due to vomiting in childhood (Axon 1995). Persons living in low socioeconomic conditions have consistently been shown to have a high prevalence of *H. pylori,* and the organism has also been found routinely in the feces of children living in endemic areas (Thomas et al. 1992). Klein et al. (1991) reported that in Peru, the water source might be a more important risk factor than socioeconomic status in acquiring *H. pylori* infection. Children whose homes had external water sources (without piped water, use a water container and bring water from a central water system to the home) were three times more likely to be infected than those whose homes had internal water sources (piped through a distribution system). Among families with internal water sources, there was no difference in *H. pylori* infection associated with income. Children from high-income families whose homes were supplied with municipal water were 12 times more likely to be infected than were those from high-income families whose water came from community wells. These findings show that substandard municipal water supplies might be important sources of *H. pylori* infection.

Escherichia coli O157:H7 is an enteropathogenic strain of *E. coli*. Infection with the organism can cause severe bloody diarrhea with abdominal cramping. In small children and the elderly, fluid replacement is of the utmost importance for a full recovery. A common more serious complication of infection with *E. coli* O157:H7 is hemolytic uremic syndrome (HUS), which causes a loss of red blood cells and kidney failure. In severe cases, HUS can cause permanent kidney damage or death. *E. coli* O157:H7 has been shown to survive similarly to typical *E. coli* strains under routine drinking water conditions. There have been two documented outbreaks of waterborne disease caused by *E. coli* O157:H7. In the 1990 Cabool, Missouri outbreak, there were 243 cases, with 32 hospitalizations and 4 deaths (Geldreich et al. 1992; Swerdlow et al. 1992). The second documented waterborne outbreak of *E. coli* O157:H7 took place in Scotland, with 496 cases (272 laboratory-confirmed cases) and 19 deaths (Dev et al. 1991). Foodborne disease appears to be more common and outbreaks affecting 700 in the western United States and 8,000 cases in Japan have occurred (Meng and Doyle 1998). Cattle (up to 57% are infected) and other ruminants are the major reservoirs; however, the pathogenic *E. coli* have been isolated from dogs, horses, swine, and cats. Contamination during slaughtering and inadequate storage and cooking are associated with the disease. Contaminated hamburger (15-40% of the lots tested) has been shown in the United States, Canada, the United Kingdom, and the Netherlands.

Salmonella typhimurium DT104 has emerged in the United Kingdom, Germany, France, Austria, Denmark, and the United States (Meng and Doyle 1998). This bacterium carries with it antibiotic resistance to ampicillin, chloramphenicol, streptomycin, sulphonamides, and tetracyclines. The number of cases has been increasing. The infection is characterized by enterocolitis (8 to 72 hours latency period) with nonbloody diarrhea and abdominal pain usually within 5 days. Hospitalization has been reported at 36% of the cases. Chronic outcomes include reactive arthritis, Reiter's syndrome, and ankylosing spondylitis. This bacterium, like other *Salmonellae,* is associated with many different foods and has been found in sheep, cattle, pigs, goats, chickens, turkeys, and domestic pets.

Campylobacter has recently been identified as the number one agent of foodborne disease. This bacterium, which can come from chickens and other animals, is prevalent in the United States and United Kingdom, according to recent surveys. This might likely be due to better diagnostics and reporting. Guillain-Barré syndrome (GBS) is a major cause of neuromuscular paralysis in the United

States, with an estimated 2,628 to 9,575 cases each year; between 20 to 40% of the cases were caused by infections with *Campylobacter* (Buzby et al. 1997). The health outcomes associated with *Campylobacter*-associated GBS have been estimated at <1% developing GBS, 20% of those requiring ventilation and 10% of those dying.

Prions

Prions are protein-based agents that are able to self-replicate and cause disease. The two that have been identified are Creutzfeldt-Jakob disease (CJD) and bovine spongiform encephalopathy (BSE). These agents cause neuropathology and death. The agents are highly resistant to heat. BSE was reported at epidemic levels in cattle in the United Kingdom with a peak of 1,200 cases per month in 1992-1993. Transmission occurs through the consumption of BSE-contaminated meat products and animal feed associated with organ supplements. CJD cases might also occur through the diet; however, the cases are rare and risk to humans has been estimated to be very low (Gale 1998; Gale et al. 1998).

Respiratory Agents

Influenza

Avian H5N1 influenza in Hong Kong served to remind the medical community of the on-going challenge in the control of influenza. Vaccine development and application will always be behind the disease curve. Although transmission from bird flocks to humans has been documented on occasion, the exact nature of the initial transmission into a community is ill-defined. Thus, exposure-prevention methods have not been readily implemented. The strong seasonality of influenza should be further investigated with regard to environmental and climatic conditions that enhance the spread of the disease. Attack rates for influenza can be high, 20 to 140/1,000, and the disease can spread quickly among contacts. An additional complication is that Guillain-Barré syndrome following influenza immunizations has been documented by the Vaccine Adverse Event Reporting System. Forty-four cases were reported in 1994 to 1995; the rate is unknown because the total number vaccinated was not reported (MSMR 1995).

A new virus in the family Paramyxoviridae in pigs has been recently described in Sydney, Australia (Philbey et al. 1998; Chant et al. 1998). Respiratory and reproductive effects in pigs were noted. Two workers in the area had an influenzalike illness with rash and serological testing showing no alternative cause, and both were seropositive for the newly described virus. Zoonotic transmission is likely, but the details of the exposure pathway have not been delineated.

Legionella

Legionella bacterium causes a severe pneumonia known as Legionnaires disease and a mild respiratory infection known as Pontiac fever. It is spread through the waterborne respiratory route; no person-to-person transmission occurs. The bacterium is usually found naturally in surface and groundwater. Surveillance data from England and Wales suggests that approximately 40% of Legionnaires cases are community-acquired and the remainder are associated with travel (Figure 5). Urinary antigen detection could be a promising new diagnostic tool that could help identify and eliminate the risk. Diagnosis and reporting are poor, particularly for mild cases. This might be an unknown and unrecognized risk for troops.

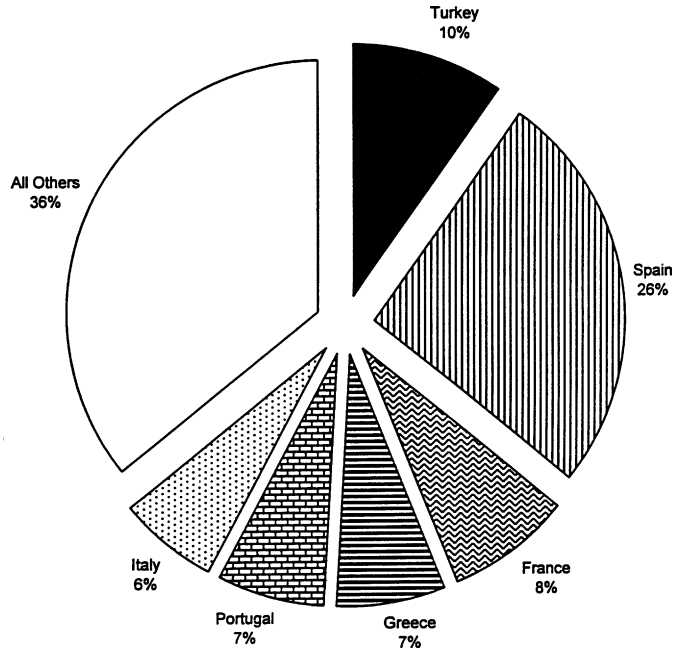


FIGURE 5 Distribution of *Legionella* cases by country visited (Joseph et al. 1998).

Skin Infections

Primary skin infections are associated with impetigo, ecthyma, folliculitis, furuncle, carbuncle, sweat gland infections, erysipelas, and erythrasmas. Impetigo accounts for 78% of all infections, generically referred to as atopic dermatitis. The major cause of skin infections are due to transient bacteria, Group A streptococci and resident bacteria, *Staphylococcus aureus,* and *Staphylococcus epidermidis*. Hypersensitivity has been identified in some cases, and vancomycin-resistant staphylococci have also emerged (Fauci 1998).

Vectorborne Agents

Perhaps more than any other category of disease, more progress has been made in understanding vectorborne diseases: the ecology of the host-parasite interactions, spread of disease, development of vaccines, and measures to prevent exposure to the vector. The worldwide spread of the vectors, the difficulty in implementing control measures, and newly identified resistant strains are challenges that continue to present themselves to deployed troops. Table 9 summarizes some of the key vectorborne diseases.

Hanta Viruses

Hanta viruses include 14 different viruses and are found throughout the world causing hemorrhagic fever and renal (HFR) syndrome in the Eurasian land mass and adjoining areas. Hanta virus pulmonary syndrome can also be found in the Americas (Schmaljohn and Hjelle 1997). Various types of rodents have been identified as vectors (mouse, rat, vole, and lemming). The viruses are transmitted to humans through inhalation of rodent excreta that contain the virus. Exposure occurs when the virus-associated excreta from soil and dust are aerosolized through indoor and outdoor activities. The diseases, previ-

TABLE 9 Major Vectorborne Diseases

Vector	Disease	Vaccine Available Or Under Development (D)
Mosquitoes	Malaria	Vaccine
	Filariasis	
	Dengue	Vaccine (D)
	Encephalitis	Vaccine
	Yellow fever	Vaccine
Ticks	Lyme disease	
	Rocky Mountain spotted fever	
	Tularemia	
Fleas	Plague	Vaccine (D)
	Endemic typhus	
Sand flies	Leishmaniasis	
Black flies	River blindness	
Bed Bugs	Chagas disease	
Rodents	Hanta virus	Vaccine (D)
	Leptosirosis	

ously known as Korean hemorrhagic fever or endemic hemorrhagic fever, have been recognized for centuries. It was not, however, until the 1950s that the western world began addressing these viral syndromes, partly as a result of 3,200 cases in United Nation forces in Korea (Gajdusek 1962).

Key characteristics in Hanta virus exposures include:

- Occurrence of outbreaks in ports-of-call.
- High virus loads in rodent population, along with increased numbers or density of rodents associated with higher risks.
- Outdoor exposures through farm work, threshing, sleeping on the ground, and indoor exposures associated with rodent infestations and inadequate cleaning.

New viruses and rodent vectors are constantly being identified. Worldwide, about 200,000 cases of HFRs involving hospitalization are reported, with the majority in China, Russia, and Korea. Mortality can be significant, ranging from 1 to 15% to as high as 40%. Given the wide distribution of rodents and their respective viruses, there appears to be a great potential for disease and continued outbreaks.

Dengue

Dengue is a severe viral illness that is spread by the mosquito *Aedes aegypti*. First described in the 1950s in Southeast Asia, the disease had, by the 1970s, emerged in the Americas in tropical and subtropical regions. This could be an emerging threat to troops that are stationed in more urban areas. It is transmitted from people to vector to people without an animal reservoir involved, and it is estimated that between 250,000 and 500,000 cases occur worldwide annually. The severity of the disease is related to sequential infection by two serotypes (Halstead 1988). Characteristics of this disease are high attack rates (70 to 80%) and high mortality rates (40 to 50%) if untreated (with appropriate treatment, mortality is 1 to 2%) (Beneson 1995; Gubler and Clark 1995).

Malaria

Malaria affects worldwide populations more than any other vectorborne disease. Up to 500 million people a year are thought to be infected; 2.1 billion are at risk (Nchinda 1998). Mortality is estimated at 1.5 to 2.7 million deaths a year. The disease is caused by the protozoan *Plasmodium* and is transmitted by the *Anopheles* mosquito. Malaria has been a concern in Africa, the Pacific, and Asia. The increasing number of cases has been related to a number of factors:

- Approximately 20 to 30% of the strains of the protozoa are resistant to chloroquine (one of the major therapies), and this is spreading.
- Population changes due to high birth rates, migration, and conflicts increases the susceptible population.
- Environmental changes in rainfall, agriculture, and urban development have led to changes in breeding habitats.
- Vector evolution and biting habits have changed.

Biological Weapons

Biological agents used as weapons will be spread through similar transmission routes as naturally occurring infectious agents. Fecal-oral microorganisms will likely be spread by contaminating the food or water supply. Indeed two incidences of intentional food contamination with *Salmonella* and *Shigella* have been reported (Kolavic et al. 1997; Torok et al. 1997). Although inhalation might be a common route of exposure for agents like anthrax, the potential to infect a large number of people by contaminating the water supply and the resistance of the spores to conventional disinfection practices should not be overlooked.

Respiratory exposure with dispersion through aerosols, using spray tanks, biological bombs, and other dispenser systems, is one of the most likely routes of transmission (Franz et al. 1997). An excellent review of biological weapons has been presented by Franz et al. (1997) (Table 10). The U.S. Army Medical Research Institute of Infectious Diseases has also published the third edition (July 1998) of the *Medical Management of Biological Casualties* (Fitzen et al. 1998) with comprehensive descriptions of agents, symptoms, diagnosis, vaccines, prophylaxis, and treatment available. Although incubation times, clinical features, and mortality rates have been described for these agents, a full quantitative assessment has not been undertaken. For example, mortality (or lethality) has been described as moderate or high without quantitative rates reported. Infectious dose is reported, incubation times, and duration of illness, but no dose-response modeling or outcome modeling has been undertaken. Vaccines are available; however, the efficacy and availability might be limited. Although certain measures can be taken to prevent biological weapon attacks, the outcome if such an attack occurs needs to be carefully evaluated so that action plans can be developed.

One of the main differences between natural and biological weapons (BW) exposures will occur in the dose, because it is likely that higher concentrations would be employed. A complete risk assessment would include the development of dose-response models from animal feeding studies (see following section on building databases). The use of dose-response models could be used directly in quantitative exposure estimates associated with the likely type of delivery systems, concentrations, and time of exposure to better predict outcomes of various BW attacks. These will be agent-specific and the effects from various attack scenarios could be examined. Plausibility evaluation, if the models could be tested, could be carried out against actual incidences in which biological weapons were used, such as the anthrax release in the Soviet Union in 1979.

TABLE 10 Some Biological Agents Used as Weapons

	Route of Exposure	Secondary Transmission	Comments
Bacterial Agents			
Anthrax spores	Respiratory, ingestion, contact	No	High mortality, 65-80% Vaccine
Brucellosis	Respiratory, ingestion, contact	No	No vaccine
Plague	Respiratory	Yes	Moderately communicable Vaccine
Q fever	Contact respiratory	No	Vaccine
Tularemia	Contact, vectorborne, respiratory	No	Moderate mortality Vaccine
Viral Agents			
Encephalitis	Respiratory	No	
Hemorrhagic fevers	Vectorborne	No	Some with moderate mortality
Small pox	Respiratory, contact	Yes	Not readily communicable Moderate to high mortality Vaccine
Toxins			
Botulinum	Respiratory, ingestion	No	High mortality Vaccine
Staphylococcal enterotoxin B	Respiratory, ingestion	No	
Plant toxin: Ricin		No	High mortality

Source: Franz et al. 1997.

One of the major concerns is the availability of vaccines in the future for agents with high mortality. These BW agents should be targeted as a priority for dose-response modeling and quantitative microbial risk assessment. Although the infectious dose and clinical outcomes have been well described, these will not be sufficient for developing the risk rankings that are needed. On the exposure side, one BW might be delivered at a greater dose for a greater duration than another. The longevity of the contamination and potential for subsequent exposure (e.g., soil) after delivery should also be accounted for. On the human health side, the ability to quickly diagnose and treat the disease, availability of vaccines, and the swiftness and consequence of the impact (morbidity and mortality) need to be considered.

Multiple Exposure Issues

In exposure assessment and dose-response modeling, single contaminant experiments and evaluations have been the primary focus of most studies. It has long been recognized that one of the major deficiencies in the application of risk-assessment protocols is the failure to consider exposure to mixtures or multiple stressors. The Gulf War syndrome has brought this issue to the forefront, and it will be necessary to address this complexity.

Exposure to multiple stressors could affect either the dose-response relationship or the health outcome. Feeding studies with enterobacteria and pseudomonads have demonstrated an increased infectivity (lower dose-response curve) associated with individuals taking bicarbonates or antibiotics. In theory, the neutral-

TABLE 11 Infectious Oral Dose for 50% of the Mouse Population for *Pseudomonas aeruginosa* (Streptomycin-Resistant Strain) Given Different Antibiotics

Antibiotic	Infectious Dose for 50% of the Population, CFU
Untreated	9.1×10^8
Ampicillin	1.7×10^7
Clindamycin	1.2×10^7
Metronidazole	3.0×10^8
Kanamycin	1.3×10^6
Streptomycin	9.1×10^4

Source: Hentges et al. 1985.

ization of stomach acids or decrease of microflora of the gut allows for infectivity to take hold, avoiding some of the nonspecific immune functions that humans employ to ward off infection.

Hentges et al. (1985) showed that antibiotics decreased the resistance of mice to intestinal colonization when inoculated orally with 10^8 colony forming units (CFUs) of *Pseudomonas aeruginosa* (Table 11). Of the mice that did not receive antibiotics, 20% still passed *P. aeruginosa* in the feces on day 14 as compared with mice treated with ampicillin (90%), clindamycin (70%), and metronidazole (50%). Buck and Cooke (1969) examined the colonization of healthy human volunteers with *P. aeruginosa* and reported that an oral dose $>1.5 \times 10^6$ CFU was required. With oral doses of 1.5×10^6 to 2.0×10^8, excretion of *P. aeruginosa* in the feces was detected for up to 14 days if the volunteer was also taking ampicillin. Excretion of the agent was limited to 6 days in volunteers not taking antibiotics. None of the volunteers experienced any disease symptoms from the *P. aeruginosa*.

Poor nutritional habits have also been linked to greater severity of health outcome after infection. The high mortality rate due to cholera in Africa as opposed to South America was, in part, suggested to be influenced by poor nutritional levels in the population.

Not only can stressors affect the infectivity of microorganisms, but invading microorganisms also can affect the absorption of other chemical stressors. Glynn et al. (1998) found that cadmium absorption increased during coxsackie B3 virus infections.

Health outcomes (the severity of illness) are also known to vary, although attack rates and dose-response do not change. Clearly, the host immune system is one of the major influences on outcome. Stressors to the immune system thus might result in more symptomatic as opposed to asymptomatic illness and more severe illness. For example, it is now known that the coxsackieviruses are associated with various forms of heart disease, eye infections, and respiratory disease. Studies in mice have shown an increased virulence (severe outcomes) associated with selenium deficiency (Beck et al. 1994). The epidemic optic and peripheral neuropathy in Cuba affecting 50,000 was associated with infections by coxsackie A9 and B4 viruses (84% of the cases) and was somewhat alleviated by supplements of B complex vitamins, vitamin A, and folate (Mas et al. 1997). Interestingly, infections with coxsackieviruses with exposure to metals has also been demonstrated to be associated with an increased risk of myocarditis (Llback et al. 1994). Toxic heavy metals (cadmium, nickel, and methyl mercury) might also affect the inflammatory character of the infection and enhance the potential for autoimmune diseases such as diabetes and myocarditis.

One of the hypotheses of the Gulf War syndrome was that the combination of vaccinations followed by the other exposures to chemical or biological agents contributed to the health effects that were observed. It is clear that at least some proportion of those vaccinated do have an adverse effect that has been recorded primarily as fever in the Vaccine Adverse Event Reporting System. Autoimmune and neurological maladies have been described with infections from *Campylobacter, Salmonella, Shigella,* and *Yersinia,* and coxsackieviruses. These have been documented with and without symptomology, that is, the outcome is due to the infection and not the level of illness. It is unclear whether infection following immunizations might enhance these outcomes in some antagonistic fashion.

Although most medical professionals (e.g., WHO and CDC) do not prescribe to the association between hepatitis B vaccination and multiple sclerosis, there have been recent court cases that have ruled that the evidence was sufficient to link the two multiple factors involved (Hepatitis Control Report 1998). The strength of the data, the risk-risk trade-off might need to be assessed before the scientifically defensible causality is definitely proven or not proven.

War syndromes from the Civil War, Vietnam War, and the Persian Gulf War have been described and show a remarkable similarity in the health problems found in troops today. The types of symptoms reported included fatigue, shortness of breath, headache, sleep disturbances, impaired concentration, and forgetfulness (Hyams et al. 1996). The other similarity is the high frequency of reported diarrhea. It is possible that this is due to unrecognized chronic syndromes (such as those reported with coxsackieviruses) or exposure to multiple stressors, mentioned above, associated with the enteric bacteria.

The disease surveillance that is currently in place can be used to examine these issues, but better exposure assessment must be undertaken. Animal models with experimentation associated with mixtures need to be developed, including mixtures of microorganisms with antibiotics, vaccinations, metals, and other infections.

RISK-ASSESSMENT AND RISK-MANAGEMENT STRATEGIES

Risk assessment might be viewed by some as a professional process that includes the participation of many established scientific disciplines. As defined in this context, risk assessment is the qualitative or quantitative characterization and estimation of potential adverse health effects associated with exposure of individuals or populations to hazards (materials or situations, and physical, chemical, or microbial agents). Risk assessment is not used in isolation, but is part of risk analysis. Risk analysis includes risk assessment, risk management, and risk communication.

The integration of risk management and risk assessment is seen as a necessary requirement in the development of a workable framework (see Figure 6). Regulatory agencies are now attempting to develop the best approach for undertaking and using microbial risk assessment for policies that will improve water quality, food safety, and public health.

The analysis phase (Figure 7) of risk assessment includes two aspects: human health effects analysis (symptomatic and asymptomatic infection; severity, duration, hospitalization, and medical care; mortality; host immune status; susceptible populations) and exposure analysis (vehicle, amount, route, single exposure versus multiple exposures over time, demographics of those exposed). Exposure analysis also includes occurrence assessment (methods, concentrations, frequency, spatial and temporal variation, regrowth, die-off, and transport). The data that ties the exposure analysis to the health outcomes quantitatively is done through dose-response modeling, with defined studies on exposures to the infectious units of bacteria, viruses, or protozoa. Quantitative information will be needed to undertake a quantitative microbial risk assessment (QMRA).

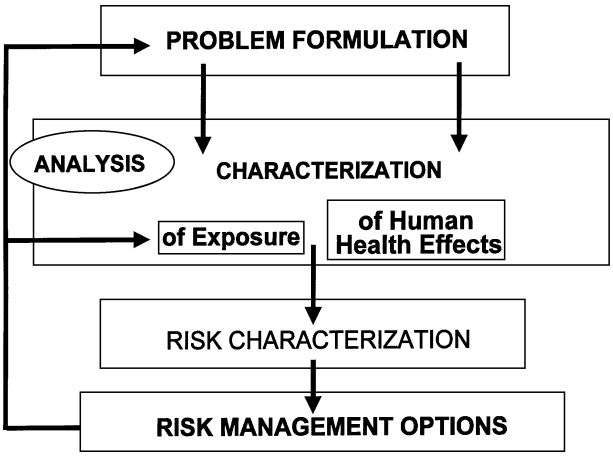


FIGURE 6 Framework for integration of risk management and microbial risk assessment. (Source: Adapted from ILSI 1996.)

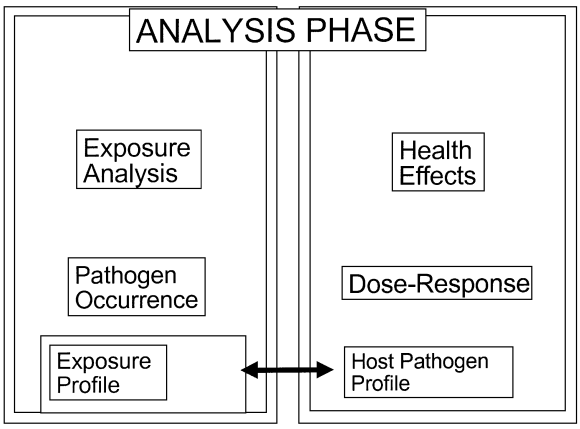


FIGURE 7 Analysis phase for microbial risk assessment (ILSI 1996).

Risk Assessment for Microorganisms

Hazard Identification

Hazard identification includes the identification of the microbial agent as well as the spectrum of human illnesses and disease associated with the specific microorganism. The types of clinical outcome range from asymptomatic infections to death. These data come from the clinical literature and studies from clinical microbiologists. The pathogenicity and virulence of the microorganism itself is of great interest, as well as the full spectrum of human disease that can result from specific microorganisms. The host response to the microorganisms with regard to immunity and multiple exposures should be addressed here, as well as the adequacy of animal models for studying human effects. Endemic and epidemic disease investigations, case studies, hospitalization studies, and other epidemiological data are needed to complete this step in the risk assessment. The transmission of disease is often microbial-specific (e.g., rabies and vectorborne diseases such as malaria or influenza); therefore, in some cases, the transmission (and to some extent the exposure) is tied into hazard identification for microbial risks. Often in these types of studies the variables are not well defined. For QMRAs, these need to be specifically described (see following section on building databases).

Dose-Response Assessment

The dose-response assessment is the mathematical characterization of the relationship between the dose administered and the probability of infection or disease in the exposed population. Dose-response assessments have been referred to as probability-of-infection models. Various doses of specific microorganisms have been given to sets of (in most cases) human volunteers. For most studies, a single dose was administered and the subjects were evaluated. The percentage of individuals infected at each dose was fit to a best-fit curve. The microorganisms were measured in doses that were obtained by counting the specific microbe in the laboratory, such as colony counts on agar media for bacteria, plaque counts in cell cultures for viruses, and direct microscopic counts of cysts or oocysts for protozoa. However, for

protozoa, this results in essentially particle counts (nonviable organisms viewed microscopically could be counted in the dose), whereas for bacteria and viruses, the opposite problem exists (viable but nonculturable organisms are not counted). Despite these limitations in estimation of the dose, the methods used are similar to those used to detect these same microorganisms in environmental samples. Natural routes of exposure were used—direct ingestion, inhalation, or contact. Both disease and infection were measured in these studies as the end point. In most cases, less virulent strains of the microorganisms and healthy human adults were used. Multiple exposures should have been evaluated, but in most studies, they were not.

Threshold Issues in Microbial Dose-Response Modeling Risk Assessment

Current scientific data support the independent-action (or single-organism) hypothesis that a single bacterium, or virus, or protozoan can initiate and produce an infection. This concept has also been suggested as providing the explanation for sporadic cases of infectious disease. Although it is clear that the host defenses (immunity at the cellular and humoral level) do play a critical role in determination of which individuals might develop infection or a more severe disease, it has also been suggested that these do not provide the complete explanation (Rubin 1987). In the early literature, it was suggested that many microorganisms were needed to act cooperatively to overcome host defenses to initiate infection. The independent-action theory, however, suggests that each microorganism alone is capable of initiating the infection, but more than one is needed because the probability that a single microorganism will successfully evade host defenses is small (Rubin 1987).

The evaluation of the dose-response data sets also support the independent-action hypothesis because in almost every case the exponential or the beta model provide a statistically significant improvement in fit over the lognormal model that could be used to predict a threshold (Haas 1983). Currently, there are no scientific data to support a threshold level for these microorganisms.

Two risk equations have been described for the variety of microorganisms. For protozoa like *Cryptosporidium* and *Giardia*, the probability of infection $\pi(P_i)$ was defined by the exponential model:

$$\pi(P_i) = 1 - e^{(-rN)}$$

where, r is the fraction of microorganisms that are ingested that survive to initiate infection (which is organism-specific), and N is the exposure. For *Cryptosporidium*, $r = 0.00467$ (95% confidence limits (CL), 0.00195-0.0097) (Haas et al. 1996). The *Giardia* risk assessment model was previously published (Rose et al. 1991) and the value for *Giardia* was $r = 0.0198$ (95% CL, 0.009798-0.03582).

Dose-response for many of the viruses and bacteria, including rotaviruses, HAV, coxsackieviruses, echoviruses, *Salmonella* and *Shigella*, have all been developed from human feeding studies (Haas et al. 1999). In these studies, the best-fit curve was the beta-Poisson model.

$$\pi(P_i) = 1 - \left[1 + \frac{d}{N_{50}}\left(2^{\frac{1}{\alpha}} - 1\right)\right]^{-\alpha}$$

The method of maximum likelihood was used to fit dose-response models to the available experimental data on the particular microorganisms. In this case, two variables, and N_{50} provided an increased goodness-of-fit over the exponential model. N_{50} may be described as the dose that results in 50% infection in the subjects exposed. Known also as the infectious-dose 50, or ID_{50}, this can be used as a comparative measure of infectivity.

Although the human data sets are extensive, they are not exhaustive in terms of answering many of the questions regarding the host-microbe interaction. Many animal data sets exist, but have not been modeled. In the future, more human and animal studies will be needed to further address both hazard identification and dose-response assessment, including virulence, strain variation, immunity, autoimmune reactions, and multiple exposures.

Exposure Assessment

The exposure assessment is aimed at determining the size and nature of the population exposed and the route, concentrations, and distribution of the microorganisms and the duration of the exposure. The description of exposure includes not only occurrence based on concentrations but also the prevalence (how often the microorganisms are found) and distribution of microorganisms in space and over time. This assessment is determined through occurrence monitoring and predictive microbiology.

Exposure assessment depends on adequate methods for recovery, detection, quantification, sensitivity, specificity, virulence, viability, and transport and fate through the environment. For many microorganisms, the methods, studies, and models are not available or have limitations in application or interpretation (e.g., detection of viable and nonviable microorganisms). Often the concentration in the medium associated with the direct exposure (drinking water, food) is not known but must be estimated from other databases. Therefore, knowledge of the ecology of these microorganisms, sources in the environment, and transport and fate are needed, including inactivation rates and survival in the environment, ability to regrow (as in the case of some bacteria) and resistance to environmental factors (temperatures, humidity, sunlight). Finally, the movement through soil, air, water, and vectors should be modeled.

Risk Characterization

Quantitative risk characterization should estimate the magnitude of the public health problem, and demonstrate the variability and uncertainty of the hazard, with four distributions: (1) the spectrum of health outcomes; (2) the confidence limits surrounding the dose-response model; (3) the distribution of the occurrence of the microorganism; and (4) the exposure distribution. Assessments of occurrence and exposure can be further delineated by distributions surrounding the method recovery and survival (treatment) distributions.

It might be possible to group microorganisms in each category by relative similarities, similar health outcomes, dose-response, or potential for exposure. In addition, parts of the risk assessment (health outcomes and dose-response models) might have applicability to many transmission routes and different exposures, particularly for fecal-oral agents (e.g., food versus water).

Setting Priorities Using Health and Exposure Data

The risk assessment framework is a scientifically-based approach that can be used to understand the hazard, define the exposure, evaluate the consequences and relative risk, address controls, and begin to evaluate unknowns and emerging threats. If used as a tool for setting priorities for the various infectious agents apart from the dose-response modeling, the data can be judged in two broad categories: exposure and health outcome.

For exposure data, the ability to control that exposure should be addressed. For health outcome data, the ability to treat the disease or immunize against it needs to be considered (Figure 8).

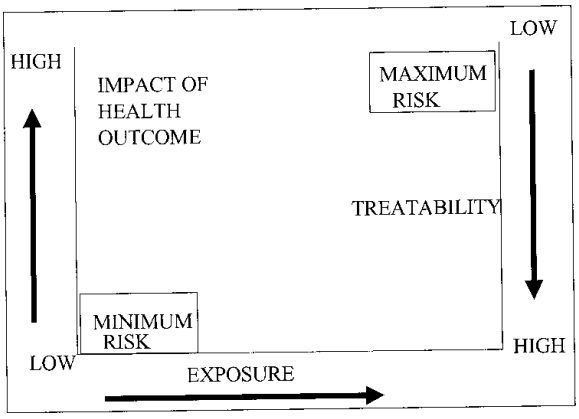


FIGURE 8 Risk matrix for infectious agents.

Thus, the approach for categorizing the risks and setting their priorities would include:

- Exposure and transmission: controls available for preventing exposure.
- Health outcomes: Vaccinations and treatment available for prevention and cure.
- Probability of infection (dose-response modeling).

Certain infectious agents might have attributes that would contribute toward a greater risk. Factors leading to higher risk might include:

- Transmission by more than one route.
- Geographic diversity.
- Zoonotic potential.
- Excretion at high numbers.
- High survival rates (resistance to environmental or engineering controls or stresses).
- Secondary and tertiary transmission.
- Low dose-response (high infectivity at low dose).
- Resistance to drugs, antibiotics.
- Unavailable or limited vaccines.
- Poor diagnostics.
- Producing chronic and acute outcomes.

The priorities would focus on those agents and illnesses (gastrointestinal and respiratory) for which there is the greatest morbidity and severe outcome and for which lack of vaccinations, poor treatment, antibiotic resistance, or poor diagnostics led to limited data. The exposure can be segregated by season, geography, and transmission (fecal-oral, vectorborne, respiratory) and would include those with the greatest potential for exposure.

Decision Frameworks

Many frameworks already exist for analysis of chemical and toxicological hazards. These frameworks, with slight modifications, would be useful for analyzing infectious agents. Figure 9 presents the risk assessment and risk management system used for the NRC toxicological program. The use of decision trees might be useful for gathering critical data to finalize the exposure assessment, even

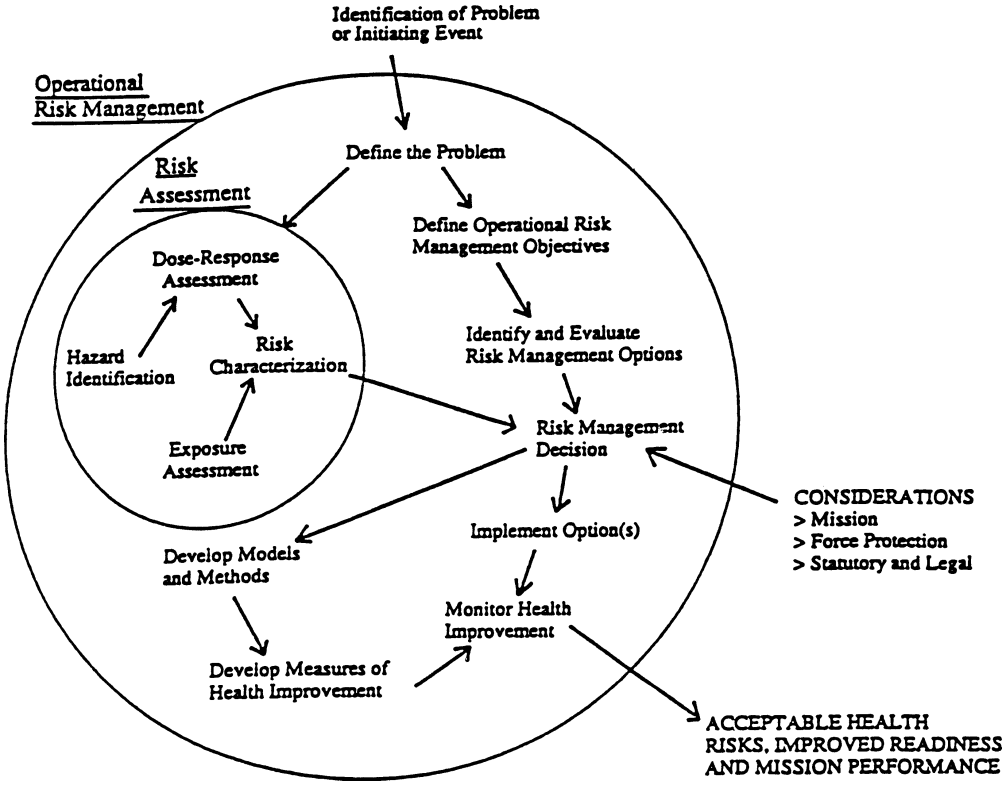


FIGURE 9 NRC risk assessment within the toxicological management scheme (Source: Adapted from NRC 1994).

without full characterization of health effects. Decision trees can be used to set priorities and eventually make management decisions for reducing the potential for exposing the population to microorganisms.

One potential framework has already been used for food safety and has been proposed for water. The hazard analysis critical control point (HACCP) system is aimed at specific operations whose ultimate goal is to ensure food safety. The physical, chemical, or biological hazard is defined, as well as the specification of the control criteria. The point at which the hazard can be controlled to acceptable levels or eliminated is then defined and is known as the critical control point (CCP). In theory, the CCP is the point at which the process or operation can be monitored to meet the performance specified to achieve the level of hazard reduction. In practice, very little has been done to implement this approach.

HACCP, when used for food safety, is food specific; therefore, the hazards and CCP might be different for beef, shellfish, or produce. Often the goal would be to establish a number of CCPs representing the entire food chain from the farm to the table with multiple barriers for protection. HACCP is a management strategy, but has elements of the risk-assessment process inherent to it. This includes some hazard identification and exposure assessment. The system is largely nonquantitative and does not incorporate dose-response or risk characterization. It can be argued that better management decisions regarding the controls, the performance standards, and monitoring can be made if a more thorough risk assessment is undertaken.

Elements in the food supply chain include production, harvest, processing, transport, packaging, storage, and wholesale and retail marketing. Finally, there is preparation in the home or restaurants. If

TABLE 12 An Example of Hazards Defined by Transmission or Exposure Potential and Control Points

Type of General Hazard or Disease By Transmission	Sources	Specific Transmission Risks	Issues to be Addressed
Fecal-oral	Humans	Foodborne	Wastewater treatment
			Agricultural practices
	Animals	Waterborne	Wildlife
			Food supply
	Birds	Person-to-person	Potable and nonpotable water treatment (individual, camp, and recycling of water)
		Fomites	Cross-contamination
			Personal hygiene
Respiratory	Humans	Direct-contact	Personal hygiene
	Birds	Airborne	Wildlife
	Water	Waterborne	Indoor ventilation
			Plumbing and piping
Vectorborne	Insects	Person-vector-person	Geographic distribution of vector and disease
	Rodents	Reservoir-vector-person	Seasonality
			Climate factors
			Behavior of vector, reservoir, and human
Contact	Humans	STDs	Behavior
	Environment (soil & water)	Skin infections: waterwashed	Use of prophylaxis
	Insects	Insect borne	Protective gear, housing clothing

this concept were applied broadly to all microorganisms of concern, then a separate systems assessment that would be hazard- and transmission-specific (e.g., for vectorborne diseases) would need to be established. The CCPs, the monitoring, and controls would also be specific. Several examples can be used to address the risk-assessment process and the relationship to HACCP (Table 12; Figure 10).

BUILDING DATABASES FOR NATURALLY-OCCURRING MICROBIAL HAZARDS AND BIOLOGICAL WEAPONS

Although health outcomes and morbidity and mortality statistics are available from numerous databases and surveillance programs, the data lacking are often the long-term assessments and chronic outcomes. However, the exposure assessment, particularly during deployment, is more suspect to uncertainty, especially in terms of quantitative evaluations.

Assessment of Health Outcome

After exposure to a microorganism and after infection begins (defined by dose-response or attack rates), the number of possible outcomes includes asymptomatic illness, various levels of acute and chronic disease (mild illness to more severe illness to chronic problems to conditions that require hospitalization) and potentially death (mortality).

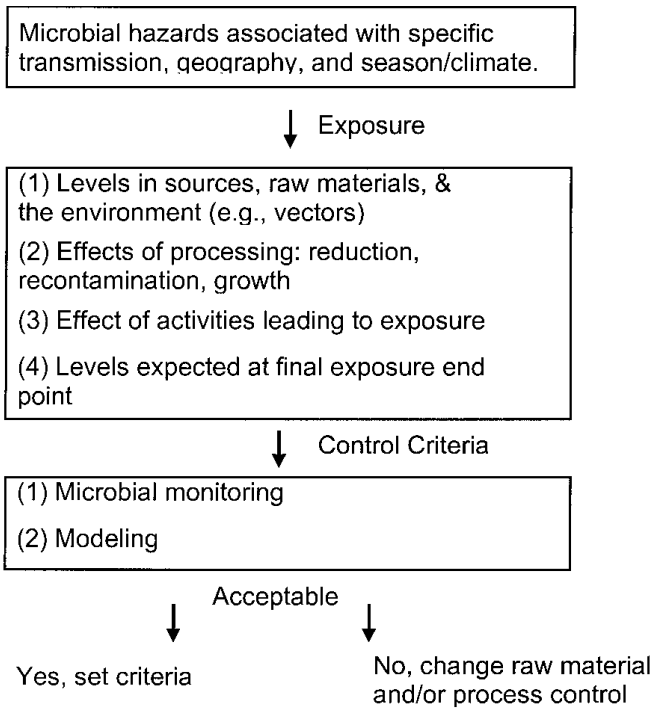


FIGURE 10 Use of risk assessment for setting criteria in HACCP (Source: Adapted from Notermans and Mead 1996).

The cases or measured rates described previously in epidemiological studies or disease surveillance of infectious diseases can be divided into several groups: (1) endemic risks that are the constant low-levels of diseases or infections that are present in a population; (2) epidemic risks that are disease cases in excess of the number of cases normally found or expected, and are constituted as an outbreak if limited to a specific population; and (3) outbreaks that are defined as two or more cases associated with a common exposure in time and place or source. In most cases, these studies rely on routine health surveillance methods, whereby the individuals seek medical attention, submit laboratory samples, and are diagnosed. Often this is done retrospectively, through the examination of records or through personal interviews and recall.

The attack rate is defined by the ratio of cases of an illness that occur relative to the total population exposed. The problem with this ratio is that often the numerator (cases) and denominator (those exposed) are not very well defined. These attack rates are not only subject to the accuracy of the investigation but are also subject to the level of the contamination (which is rarely identified), concentration of the microorganism in the exposure medium, frequency of exposure, and type of microorganism (dose-response). However, it appears that at least in drinking-water outbreaks (perhaps under conditions of lower levels of contamination), it is the microbial hazard that influences these attack rates, which correlate well with the dose-response values for the individual microorganisms (Figure 11). For example, on average, 22% of the populace in the communities exposed developed illness when the drinking water was tainted with *Campylobacter,* and 53% of the populace became ill during waterborne outbreaks of the Norwalk virus.

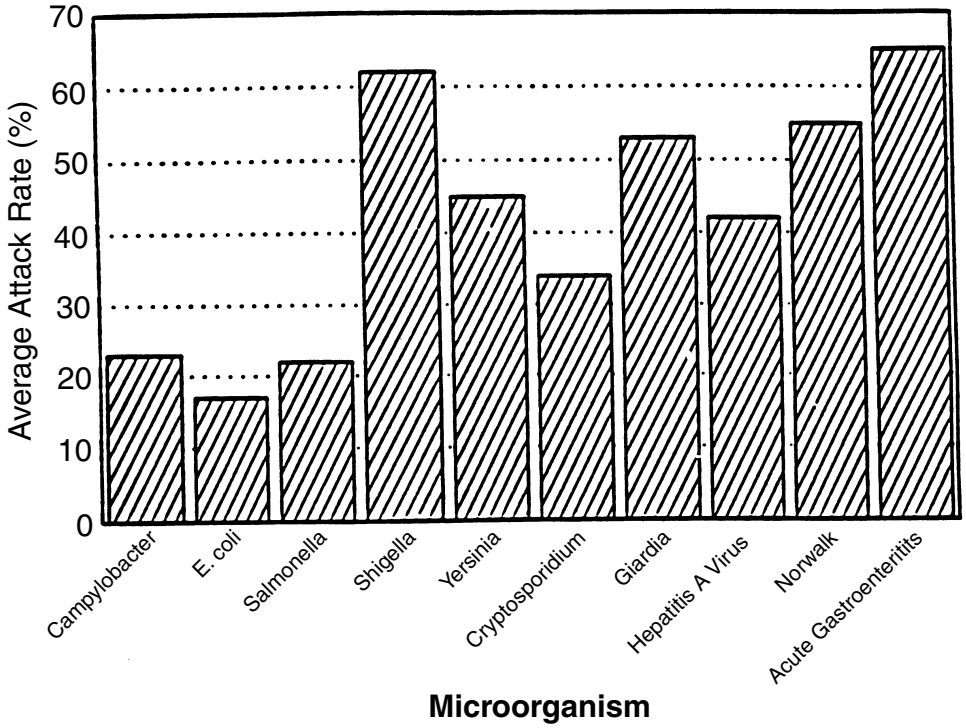


FIGURE 11 Average attack rates by microorganism during waterborne outbreaks. (Source: Haas et al. 1999.)

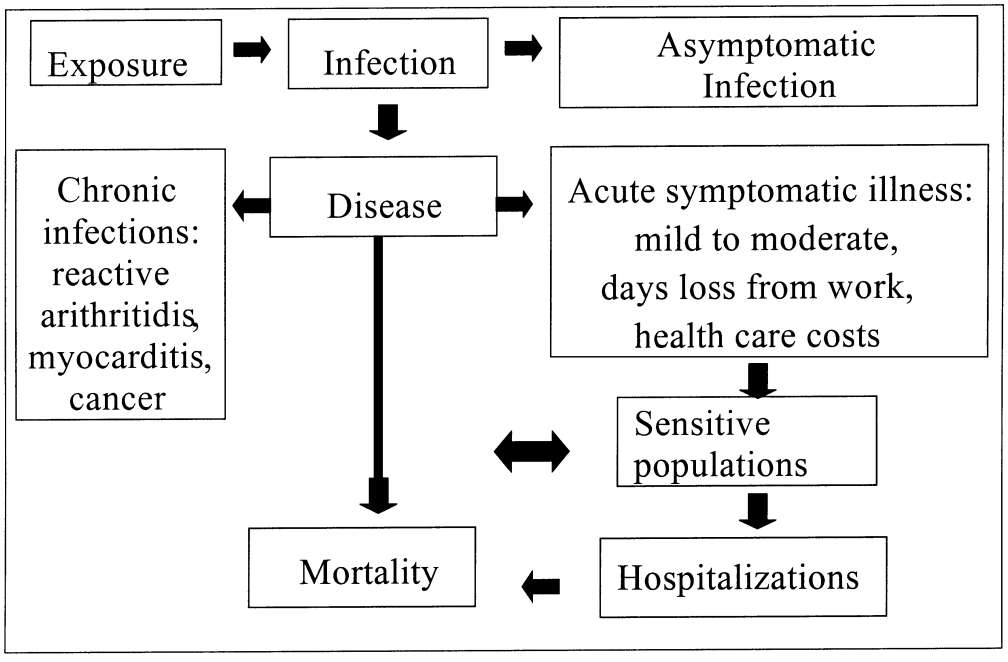


FIGURE 12 Outcomes of the infection process for quantification. (Source: Haas et al. 1999.)

Figure 12 demonstrates the various outcomes that need to be assessed during exposure and infections. It has been difficult to predict, based on the current health databases, the quantitative probability of each possible outcome because it might be microorganism-specific, even isolate-specific, and can depend on the host's status. The goal of hazard identification, however, is to define these outcomes to the extent possible. Each outcome can be described as a ratio or percentage, but the numerator and denominator need to be adequately defined, as well as the populations that are associated with the data.

Health Outcome Databases Associated With Biological Weapons and Terrorist Attacks

Figures 13 and 14 demonstrate the outcomes of the *Salmonella* and *Shigella* outbreaks associated with the tainted food sources during suspected terrorist acts (Torok et al. 1997; Kolavic et al. 1997). During the *Salmonella* event, lettuce was contaminated at several restaurants. Employees and customers were exposed. For employees, infection was determined by clinical diagnosis based on excretion of the bacteria in the feces for those with no symptoms, or mild symptoms, and by self-reporting at least three (reporting symptoms of fever, chills, headache, nausea, abdominal pain, vomiting, or bloody stools), for those with case-definition symptoms. Based on this, a 53% attack rate was established and could be used to estimate the impact of the contamination (692 cases/0.53 = 1,306). With 53% and 32% being the illness rate and infection rate, respectively, the estimate of the total number affected would be ~ 4,081 (1,306/0.32). There was no estimate of the number of individuals exposed. Severity was shown to be 6.5%, based on hospitalizations (45/692). There were no deaths. Although chronic outcomes were not followed, secondary transmission was estimated at 1%. In contrast, the *Shigella* event involved very high levels of contamination of muffins that were consumed by 12 individuals (although 45 people had access to the muffins), all of whom became ill (100% attack rate). The illness was more severe with 42% and 30% visiting the emergency room and being hospitalized, respectively. No deaths occurred and no chronic outcomes were evaluated.

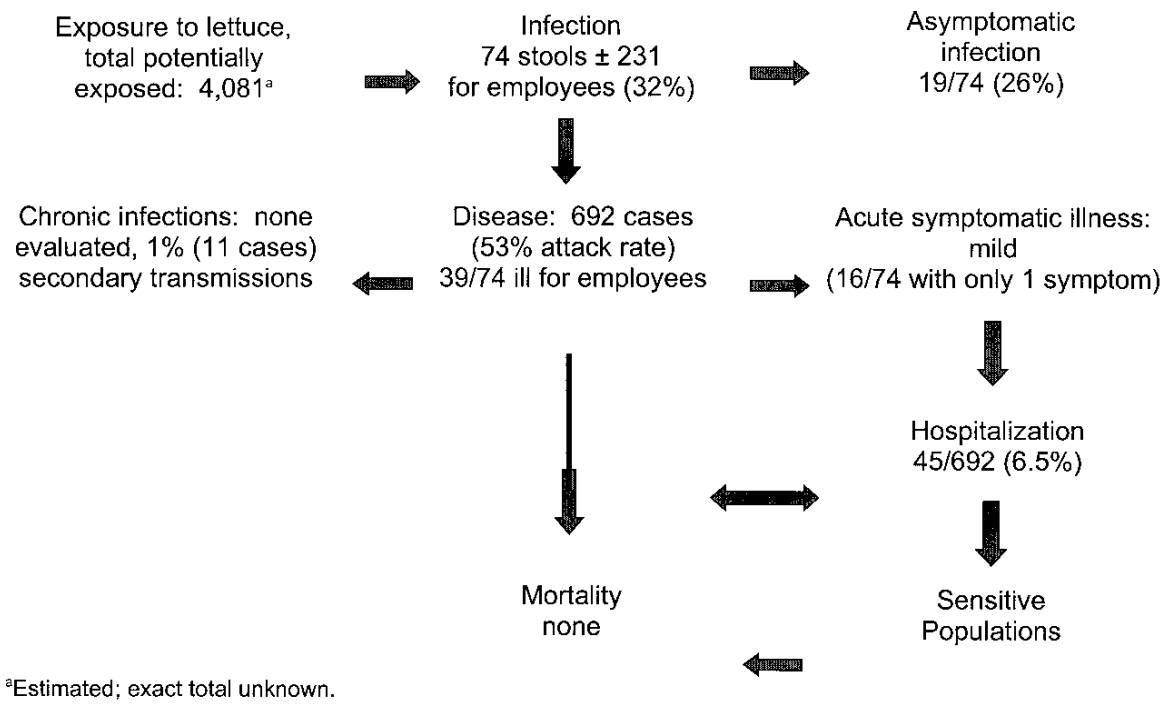
Figures 15 and 16 show the dose-response models for the two bacteria. *Shigella* (N_{50} = 1,120; hospitalization 30%) has a greater infectivity and severity than *Salmonella* (N_{50} = 23,600; hospitalization 6.5%). However, the magnitude of the *Salmonella* outbreak is greater (45 hospitalized compared with 4 in the *Shigella* outbreak) due to the amount and nature of the exposure (more people, multiple days, and multiple restaurants). The dose-response models could determine the average dose from the outbreak data, by setting the attack rate (4,081 infected/total exposed) equal to P_i and then solving for N. These types of quantitative assessments allow the building of exposure scenarios whereby thresholds associated with ineffectiveness in the troops in a given time frame can be determined for specific agents.

Table 13 shows some of the other data that would be required in determining health outcomes.

Assessment of Exposure

Critical to the risk-assessment processes is the ability to quantify exposure to pathogens. Methods used in environmental applications are available to isolate and identify bacteria, fungi, protozoa, and viruses, as well as microbiological toxins (Hurst 1997). Standard methods have and continue to be used, such as those published in *Standard Methods for the Analysis of Water and Wastewater* (APHA 1998). However, newer methods using immuno-magnetic capture systems and molecular techniques are now being applied to foods for detection of *E. coli* 0157:H7 in hamburger.

Much of the past microbial occurrence data are nonquantitative, reported as presence or absence, and developed with very different protocols and monitoring approaches. Thus, often the issue is not the



[a]Estimated; exact total unknown.

FIGURE 13 Outcomes associated with an intentional contamination of *Salmonella* leading to an outbreak. (Source: Torok et al. 1997.)

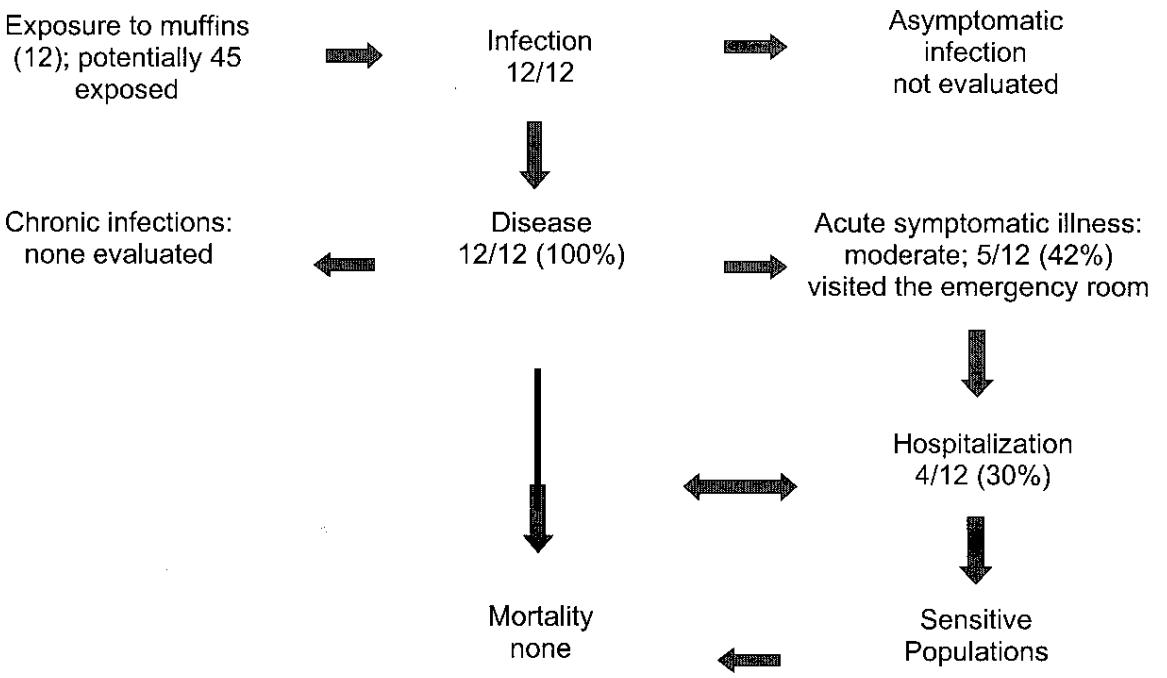


FIGURE 14 Outcomes associated with an intentional contamination of *Shigella* leading to an outbreak. (Source: Kolavic et al. 1997.)

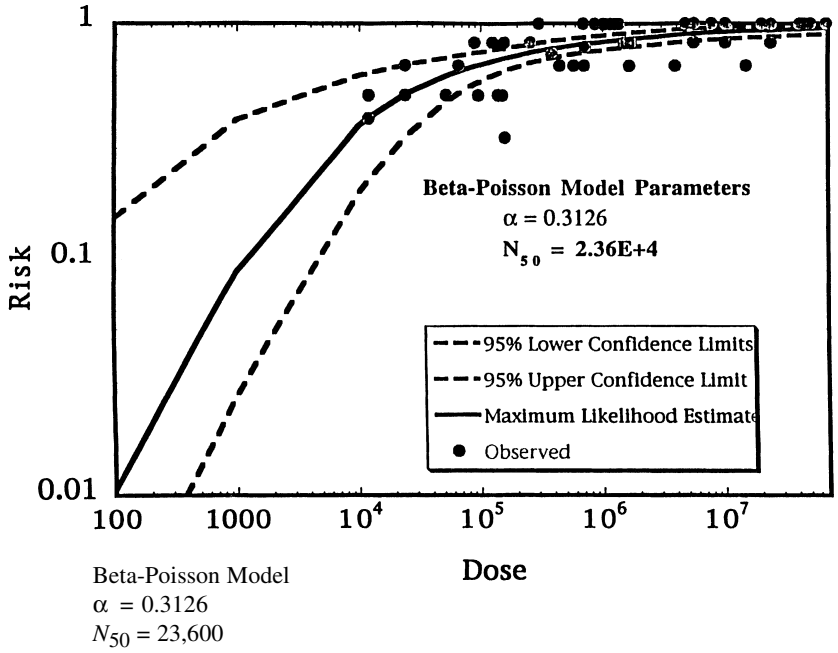


FIGURE 15 Dose-response model for *Salmonella*. (Source: Haas et al. 1999.)

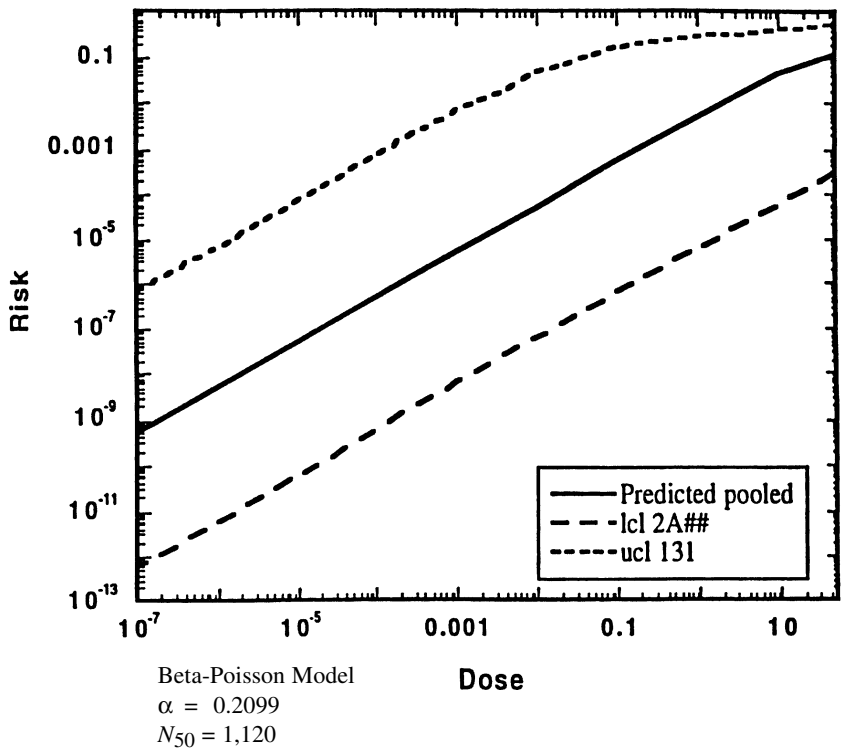


FIGURE 16 Dose-response model for *Shigella*. (Source: Crockett et al. 1996.)

TABLE 13 Assessment of Health Outcome[a]

Health Effects	Data Needs
Evaluation of outbreaks	Magnitude of community impact, attack rates, hospitalization and mortality, demographics, sensitive populations, level of contamination, duration, medical costs, community costs. Course of immune response and secondary transmission. Follow-up long-term outcomes.
Evaluation of endemic disease	Incidence, prevalence, geographic distribution, temporal distribution, percentage associated with various transmission routes (e.g., water versus food), demographics, sensitive populations, hospitalization, individual medical costs. Antibody prevalence, infection rates and illness rates.
Immune status	Protection versus issues for depression of the immune system.
Description of microbial pathogens	Mechanism of pathogenicity (how does it cause disease), virulence factors, virulence genes, antibiotic resistance.
Disease description	Types of diseases, duration, severity, medical treatment and costs, days lost, chronic sequelae, contributing risks (i.e., pregnancy, nutritional status, lifestyle [i.e., smoking and *Legionella*], immune status).
Methods for diagnosis	Available, routinely in use, require special requests, ease in use, cost, time.

[a]Clinical diagnostic tests must be available before other databases can be adequately established.
Source: Haas et al. 1999.

detection method per se but the sampling protocols and schemes and the interpretation of the data. These data have limited application for quantitative risk assessment. It is now recognized that quantitative, statistically evaluated databases must be developed because lack of exposure databases is often the major data gap for adequate risk assessments. These databases must be combined with models for prediction of transport and fate of microorganisms through the environment and through water and food treatment processes. By doing so, the field of predictive microbiology is a rapidly developing area that will be able to fill some of the data gaps on exposure assessment.

Exposure assessment could be defined as monitoring the source of the exposure over time, up to contact, that is, the final food product prior to consumption, the glass of water from the tap, or the aerosol that is inhaled. This is a difficult and impossible task in most cases. Microorganisms, unlike chemicals, act as particles, and their concentrations in water, soil, air, food, and on surfaces are not normally or homogeneously distributed. Microorganisms can change concentrations through die-off or growth over time. The sources of the microorganisms (e.g., animal wastes or sewage) are also diverse in concentrations over time (e.g., seasonal and climatic influences). Finally, many controls have already been implemented (disinfection) to reduce the concentrations and the exposure. Therefore, other strategies have been developed for assessing exposure and developing occurrence databases for microorganisms. These include the monitoring of indicators and pathogens for

- assessing the sources of microorganisms,
- assessing the transport and fate of microorganisms, and
- assessing the reduction through the use of treatment and process controls of microorganisms.

These approaches include field data and laboratory-based data and the use of models for evaluating transport (e.g., subsurface migration) and fate (e.g., inactivation rates). Ecosystem studies are necessary for evaluating most microorganism transport and fate (e.g., *Legionella* in biofilms and release during

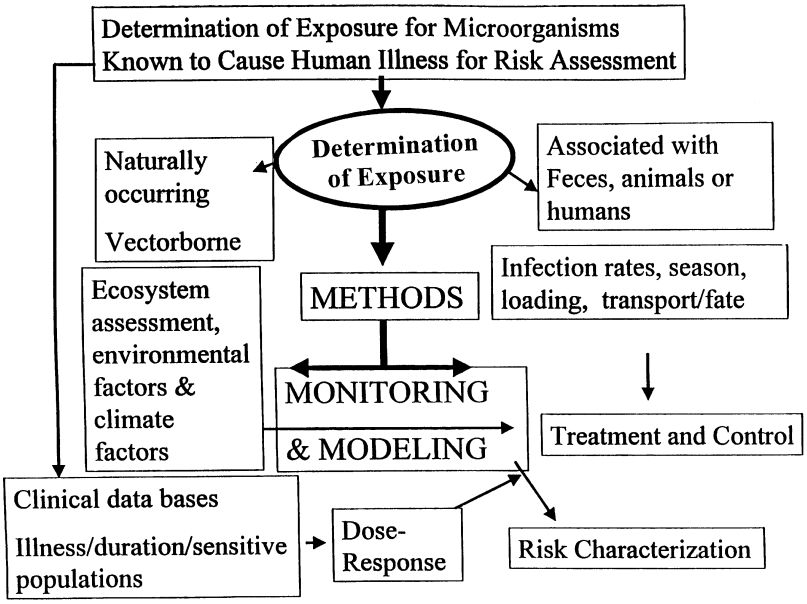


FIGURE 17 Framework for determination of exposure.

aerosolization), and more ecosystem modeling is needed. In the area of food safety, the concept of farm-to-table is being used to follow the microbial contaminants from their source on the farm through harvest and production to the final packing of the food product. For drinking water, a similar system based on watershed assessment, drinking-water treatment efficacy, and distribution-system integrity is being promoted. In some of these cases, an understanding of infections in the animal or human populations, waste disposal practices, and the transport patterns, survival, and growth of the microorganisms must be gained and monitoring data must be developed to support the likelihood of exposure through the various pathways. Therefore, the evaluation of exposure will require the extensive development of a variety of databases and models.

Figure 17 shows an example of how the exposure determination is tied to the risk assessment.

Assessment of Dose-Response and Disease Modeling

There have been over 40 dose-response data sets analyzed to date (Haas et al. 1999). Tables 14 and 15 show a summary of some of these data and Figure 18 shows a comparison of the models.

The development of a quantitative dose-response relationship is a primary step in performing a risk analysis. In QMRA microbial risk assessment, the dose-response relationship enables estimates to be made of the likelihood of an infection occurring, that is, the ability of the microorganism to colonize the body, specifically in the intestinal tract or the respiratory tract, for example. In the environment, exposures to microorganisms are usually at doses that are too low to measure via direct dose-response experiments. The exceptions to this are with BWs and bacterial growth in foods. In addition, microbial toxins may be modeled more as a chemical dose response than a microbial but very little data on toxins have been modeled to date.

TABLE 14 Best-Fit Values for Some Fecal-Oral Microorganisms

		Best-Fit Model Values		
		Exponential	Beta-Poisson[a]	
Microorganism	Subject (doses)	k	α	N_{50} (β)
E. coli	Human (19)	na	0.1748	2.55×10^6
Campylobacter	Human (6)	na	0.145	896
Salmonella nontyphoid	Human	na	0.3126	2.36×10^4
Shigella	Human (13)	na	0.2099	1.12×10^3
Cryptosporidium	Human (8)	238	na	
Giardia	Human (9)	50.2296	na	
Coxsackie B viruses	Mice (4)	129	na	
Rotavirus	Human (8)	na	0.265	5.597

[a]Using a modified Beta-Poisson model: $P_i = 1 - [1 + N/\beta]^{-\alpha}$.
Source: Haas et al. 1999.

TABLE 15 Best-Fit Parameters for Additional Microorganisms

		Best-Fit Model Values		
		Exponential	Beta-Poisson	
Organism	Subject (doses)	k	α	N_{50}
Adenovirus	pigs (3)	3375.3500	n/a	n/a
Adenovirus *type 4*	pigs (3)	267.0500	n/a	n/a
Astrovirus	humans (3)	16.5×10^5	n/a	n/a
Conjunctivitis[a]	humans (6)	38.5×10^1	n/a	n/a
Conjunctivitis[b]	humans (4)	8.3700	n/a	n/a
Conjunctivitis[c]	humans (12)	n/a	.4041	1.11
Cyanobacteria	mice (8)	23.7×10^1	n/a	n/a
Echovirus	humans (3)	78.3×10^1	n/a	n/a
Endamoeba coli	humans (5)	n/a	.1008	34.1×10^2
Influenza type 2	humans (5)	77.9×10^5	n/a	n/a
Influenza type 3	hamsters (9)	4.8301	n/a	n/a
Porcine enterovirus[d]	pigs (3)	3375.3500	n/a	n/a
Porcine enterovirus[e]	pigs (3)	267.0500	n/a	n/a
Rhinovirus type 14	humans (6)	n/a	.2011	9.22
Rhinovirus type 39	humans (5)	n/a	.2245	3.29
RSV[f]	humans (3)	15.0×10^4	n/a	n/a
RSV	humans (7)	n/a	.1639	41.9×10^4
RSV	primates (6)	n/a	.1136	86.8×10^4
Rubella	humans (2)	94.6000	n/a	n/a

[a]IC Cal strain.
[b]IC Cal 8 YS10 strain.
[c]IC Cal 8 YS10 and IC Cal 8 strain.
[d]PE3-ECOPO-6 strain.
[e]PE7-O51 strain.
[f]Respiratory Syncytial Virus.
Source: Haas et al. 1999.

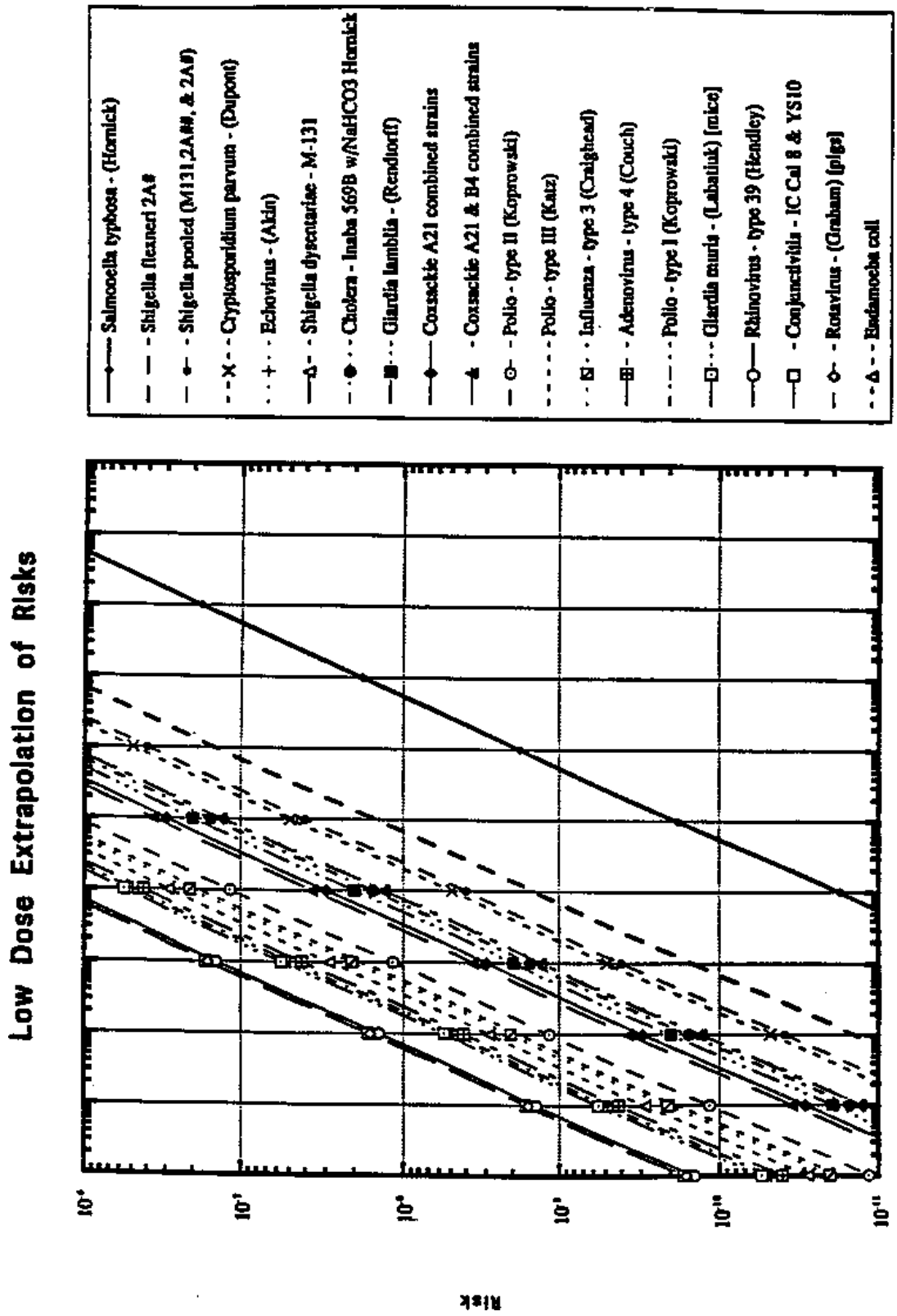


FIGURE 18 Comparative dose-response models at low-level exposure. (Source: Haas et al. 1999.)

Methodological Issues and Types of Data Sets

Obtaining data from a study designed to test the dose-response relationship of a specific organism on a human host is the ideal situation. However, it will be necessary at times to use data from studies designed for animals. Besides extrapolation from animals to humans, other issues identified in building databases include:

- How the dose was administered. This includes information about the type of system that was used to measure and administer the dose.
- Identification of the criteria used for a positive response. In most cases colonization was the criterion used, referred to as infection (clinical diagnosis or antibody response [serology]).
- The number of exposures.
- High-dose experiments without low doses tested.

Data can be pooled from many studies, as was the case for the *Shigella* and *Salmonella* models, or there might be a single study that would lead to the model. With either approach, upper and lower confidence limits can be determined for the models.

Both infection and the development of symptomatic disease can be measured, but in many experimental data sets not all the pertinent information is reported. However, there are several studies that do measure both, and in these situations a morbidity analysis can be performed (dosages required for infection to result in illness). In some cases, the illness was independent of the dose (such was the case for *Cryptosporidium*, Haas et al. 1996).

The data demonstrate that once infection had occurred the microorganism had some inherent virulence, that is, for example, 50% of those who became infected became ill.

As an example of infectivity, one might examine the data on the Hanta virus (Haas, C.N., Drexel University, Philadelphia, Penn., personal communication, 1999). The Hanta virus is transmitted through the aerosolization of the virus from urine from infected rodents. (As one of the types of viruses that cause hemorrhagic fever, it has also been placed on the list of BWs.) The infectivity of this virus can be modeled based on data reported by Nuzum et al. (1988). Mice were the host used and the dose was given in a single exposure by nasal aerosolization. Seroconversion (antibody response) was used as the measure of infectivity. The beta-Poisson model is shown in Figure 19. The data demonstrate that this virus is highly infectious. Interestingly, the inability to fully characterize the dose based on current methodologies was shown, because less than 1 PFU (plaque forming unit, the culturable unit for measuring viruses) could initiate the infection and the serological conversion. Morbidity, severity, mortality, and the other outcomes previously discussed would need to be further assessed.

Vectorborne Disease Modeling

Climatic issues have spurred the development of models for predicting disease outcomes associated with vectorborne transmission and changes in temperature and precipitation, particularly for malaria and dengue (Martens et al. 1994; Patz et al. 1998). These models combine elements of population epidemiological modeling as the outcome assessment associated with exposure to the infected vector (Figure 20). The density of the vectors, their age, their infectivity, and biting frequency can be predicted based on environmental conditions associated with precipitation and temperature. Thus, although not traditional

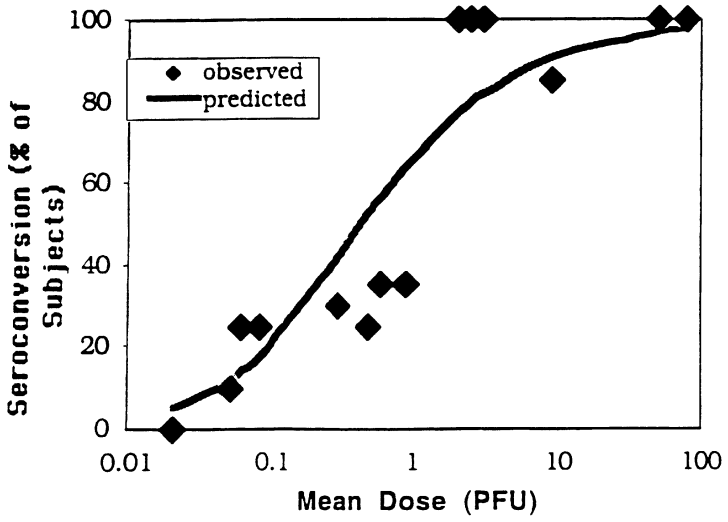


FIGURE 19 The beta-Poisson dose-response model for Hanta virus. (Source: based on the data of Nuzum et al. 1988.)

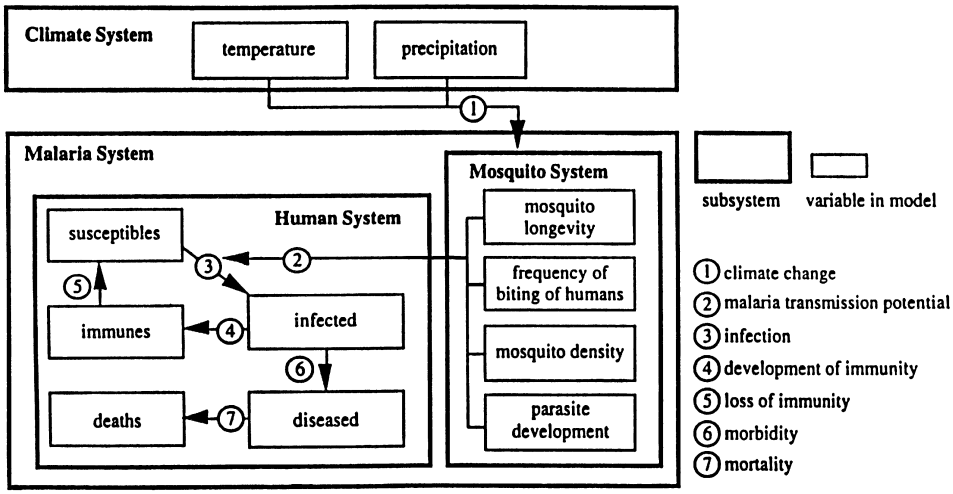


FIGURE 20 Disease model for malaria. (Source: Martens et al. 1994.)

dose-response models, these climatic models are extremely useful for comparing risks to various populations and could be used to examine the risks to deployed troops. Data should be gathered on geographic and climatic conditions, along with knowledge on the distribution and density of the vector and the level of infection of the parasite in the vector. Rapid methods (using molecular techniques) for assessing the level of virus or protozoan present in the vector population could be used in modeling the potential risk redeployment.

DOD INFECTIOUS DISEASE RESEARCH LABORATORIES

Summary of the Laboratories' History and Missions

There are nine DOD infectious disease research laboratories, three in the Washington, DC, area in the United States and one in each of the following countries, Peru, Brazil, Kenya, Egypt, Indonesia, and Thailand. Table 16 is a brief summary of the laboratories.

Early in the history of the United States, it was clearly recognized that conflicts, wars, and deployment of troops carried with them special medical needs in regards to infectious disease. No doubt the high morbidity and mortality associated with early conflicts such as the Civil War led to the realization of the importance of disease in these situations. In the late 1800s and early 1900s, great strides were being made in science and medicine. Methods were being developed for diagnosing diseases and characterizing microorganisms. There was a greater understanding of the disease process and transmission, and vaccines were being developed. In 1893, the Army Medical School was established to train physicians in the art and science of military medicine. Now known as the Walter Reed Army Institute of Research (WRAIR), this is the oldest and largest facility.

The current mission of the WRAIR is "biomedical research focused on soldier health and readiness." Early in its history, the development of a vaccine for typhoid fever and the study of yellow fever by Major Walter Reed in Cuba during the Spanish-American War were major accomplishments that led to a recognition of the benefits from such an organization. Since that time WRAIR has been involved in addressing the key plagues of the troops (such as malaria, hepatitis, dysentary, dengue) from WWI through the Bosnian conflict. Vaccine development, treatments, diagnostics, surveillance, assistance with deployments, and education have remained key components of the facility. Infectious diseases, combat casualty care, army operational medicine and medical chemical and biological defense are the four areas where research is conducted.

Although WRAIR is the largest laboratory within the U.S. Army Medical Research and Materiel Command, three other units were established outside of the United States. The largest of the three, the Armed Forces Research Institute of Medical Sciences (AFRIMS), functions as a Special Foreign Activity of the WRAIR. Established in 1959 in Bangkok, Thailand, the original mission was to research the cholera epidemic as was a part of the Southeast Asia Treaty Organization Cholera Research Laboratory. Command is with the Royal Thai Army and joint research on tropical diseases has included studies on Japanese encephalitis, hepatitis A and E, dengue, diarrhea, malaria, and drug-resistant scrubtyphus. The scientists have also been responsible for field-testing new drugs and vaccines. Epidemiological investigation, surveillance, rapid diagnostics, and advice on tropical diseases are part of the primary objectives of the laboratory.

TABLE 16 Rate of Infection and Clinical Cryptosporidiosis

Dose of oocysts	Exposed	Infected	Ill
30	5	1	0
100	8	3	3
300	3	2	0
500	6	5	2
>1000	7	7	2

Source: DuPont et al. 1995

Two smaller laboratories, known as U.S. Army Medical Research Units (USAMRU) were established, Unit K in Nairobi, Kenya, in 1969 and Unit B in Brazil (Rio De Janeiro and several other satellite locations) in 1973. U.S. personnel are limited at these facilities and they house host-country scientists and medical personnel. USAMRU B collaborates with PAHO, Institute of Biology of the Brazilian Army, University of Espirtu Santu, Vitoria and Instituto de Medicina Tropical do Amazonas to study emerging infectious disease agents in the Brazilian Amazon. The USAMRU K is affiliated with the Kenya Medical Research Institute and works out of two main facilities, a central laboratory in Nairobi and a field laboratory in Kisumu/Kisian in western Kenya. There are many joint collaborations with other organization including the U.S. Centers for Disease Control (CDC) and the Japanese International Cooperative Agency. The research has focused on drug resistance and vectorborne disease (tryptosomiasis, leishmaniasis, arboviruses). Molecular techniques such as PCR are used for microbial detection and characterizations and the facility houses a rearing laboratory for sand flies and mosquitoes.

Originally established in 1956 and officially named in 1969, the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) was established in Ft. Detrick, Maryland. This is the second largest Army facility with approximately 450 scientists and other personnel. Their mission is to "conduct research to develop strategies, products, information, procedures and training programs for medical defense against biological warfare threats and infectious diseases." The research here is focused on deployment, and special scientific teams are developed and dispatched to assist in various types of investigations. The facility has one of the few biological level (BL)-4 containment laboratories to work on highly infectious and deadly diseases. The research is focused on biological weapons in addition to other areas including vaccine and drug development. The Navy Medical Research Institute (NMRI) was established in 1942 and is located in Washington, D.C. During the war NMRI's mission was focused on immediate operational problems and in particular was commissioned to study the atomic bomb survivors and develop methods for treatment of radiation exposure. The facility housed the first tissue bank in the world and pioneered studies on freeze-drying techniques used in preservation of human tissues for grafting and use of hypothermia for open-heart surgery. Among the recent accomplishments, scientists have also developed handheld assays for identification of BWs, and a PCR-based diagnosis system for *Campylobacter.* The NMRI and the WRIAR work as co-tenants (as a combined Army-Navy medical research program) and will soon be housed in a new facility in Forest Glen, Maryland.

In 1940 and 1942, Naval Medical Research Units (NAMRU) 2 and 3 were established in Guam (relocated to Taipei, Thailand) and Cairo, Egypt, respectively. Unit 2 is focusing on significant diseases in Asia, and is a WHO-collaborating center for emerging infectious diseases. Because it houses an animal facility, research on hemorragic fevers is of interest. Unit 3 has historically studied rickettsial disease, cholera, smallpox and meningitis, but has begun examining drug-resistant malaria, enterotoxogenic *E. coli*, *Campylobacter, Shigella,* and emerging viruses. This unit is also a WHO-collaborating facility for the study of the new strains of cholera and also has an animal facility.

Finally, in 1983, the Naval Medical Research Institute Detachment (NMRID) was established in Lima, Peru (10 years after USAMRU B in Brazil). Antibiotic resistance and drug-resistance in malaria were of interest and the research moved to address the dengue virus using PCR. This laboratory also contains an animal facility.

DOD Global Emerging Infectious Surveillance and Response System

The formal expansion of DOD's mission on emerging infectious diseases in June 1996 by Presidential Decision Directive NSTC-7 now includes global surveillance, training, research, and response. A 5-year strategic plan has been developed in parallel with CDC. Four goals have been articulated and are described in Table 17.

TABLE 17 DOD Infectious Disease Laboratories

Lab	Date Established/Location	Approximate Personnel Level	Focus and Special Activities
Naval Medical Research Institute Detachment (NAMRID	1983; Lima, Peru	8 Americans	Animal laboratory facility Antibiotic resistance Malaria drug resistance PCR: dengue
Naval Medical Research Unit 2 (NAMRU2)	1940; Guam then relocated to Taipei, Thailand (Indonesia)	21 Americans 120 Indonesians	Infectious disease Military significance in Asia WHO collaborating Center for Emerging Diseases of S.E. Asia
U.S. Army Medical Research Unit B (USAMRUB)	1973; Rio de Janeiro, Brazil and satellite locations limited	15 Brazilians U.S. personnel	Animal laboratory PAHO U.S. Collaborating
Naval Medical Research Unit 3 (NAMRU3)	1942; Cairo, Egypt	19 Americans 165 Egyptians	Rickettsia Cholera Smallpox Meningitis Emerging viruses Drug-resistant malaria Enterotoxogenic *E. coli*/*Campylobacter*/*Shigella* Animal facility WHO collaborating (19 personnel) CDC-Cholera OB9
U.S. Army Medical Research Unit K (USAMRUK)	1969; Nairobi, Kenya	8 Americans Kenyan personnel of the Medical Research Institute	Drug-resistant malaria Tryptosomiasis Leishmaniasis Arboviruses Viral infections CDC/Japan International Cooperative Agency PCR (insect facilities)

Armed Forces Research Institute of Medical Science (AFRIMS)	1959; Bangkok, Thailand	Numbers not given (largest of the USAMRU)	Cyclospora Diseases Scrubtyphus Malaria Hepatitis Diarrhea Dengue Japanese encephalitis Risk assessment New drugs/vaccines/diagnostics PCR Flow cytometry Animal facility
U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID)	Ft. Detrick, MD	450 Americans	Deploy teams for investigation Vaccines/drugs BW Biological lab Level 4 (BL 4) Lab
Naval Medical Research Institute (NMRI)	1942; Washington, D.C.	Numbers unavailable	Navy tissue bank Operational problems Radiation study Handheld devices for BW PCR
Walter Reed Army Institute of Research (WRAIR)	1893; Washington, D.C.	700 Americans	Biomedical research Vaccine development Treatments, diagnostics, surveillance Assistance with deployments Infectious diseases Combat casualty care Army operational medicine Medical chemical and biological defense

One of the major assets in implementing this new directive is the overseas research laboratory system that is currently in place. All of the laboratories are undertaking various aspects related to all four goals. Clearly, although geographic locale is of some interest for some of the diseases, there is widespread global distribution of many of the microbial hazards. New resources will likely be needed to enhance not only the laboratory infrastructure and equipment but also to address personnel gaps. The evaluation and assessment of each laboratory is needed. Although specific activities matched to each laboratory's capabilities have been identified under each of the goals, there is no formal process for identifying and setting priorities for the various hazards, the specific activities, and the resources distribution. The use of risk-assessment methodologies offers an opportunity to use a scientific-based process for identifying and setting priorities for the most efficient and productive allocation of resources to the overseas laboratories.

Opportunities for Research Using a Risk-Assessment Method

It is proposed that a risk-assessment framework be used to develop criteria documents or briefs on the various microbial hazards, dose-response models, exposure assessments, and risk characterization, followed by a risk-management strategy. These documents can be used to fill data gaps and then be matched to the capabilities of the various laboratories. Clearly, laboratories with animal facilities could begin to fill gaps on dose-response and mixtures data. Laboratories with insect facilities can further evaluate the vectorborne models that have been developed. The overseas laboratories involved in treatment and vaccine development will fall into a category associated with risk-management research. However, one of the greatest needs will be to adapt the available tools to quantitate the hazards and, in particular, the exposure assessment in a prospective manner.

Environmental health programs focusing on exposure assessment using modeling and monitoring data will need to be developed. Data on the quality of food, water, air, and environment (surfaces) and health surveillance of the people will be needed. This will spur the development of better methods for environmental monitoring and lead to evaluation of the current tools. At a minimum, each laboratory staff should be trained in risk-assessment methods, should have PCR capabilities, and be trained in the use of the Geographical Information Systems (GIS) for maintaining and analyzing the database.

LESSONS LEARNED AND RECOMMENDATIONS

Lessons Learned from Deployments and Disease Surveillance

1. Intestinal illness and upper respiratory infection remain one of the greatest threats to deployed troops. These are largely of an unknown etiology and the hazards have not been properly identified. The illnesses are also time-dependent, with the greatest risk associated with early deployment.

2. There is seasonality and geographic variation in the diseases, although the factors associated with these trends are often not known.

3. Indigenous foods, fruits and vegetables, and bottled waters are associated with gastrointestinal risks.

4. The indoor environment is associated with upper respiratory illness.

5. Despite vaccination programs, with evolution will come new strains of pathogens that will continue to emerge (e.g., influenza) causing illness in troops. Assessment of these episodes will provide insight into the spread of disease globally.

6. Although vectorborne disease remains a concern, predeployment assessment of risk and preven-

tion has been shown to be successful; however, diligence is needed because exposures as low as a few hours can result in serious illness.

7. Although much is known about types of biological weapons that could be used, concerns regarding availability of vaccines has emerged, as well as the ability to detect and respond to an attack.

8. Some emerging infectious diseases are being studied and assessed in troops; however, the data are limited. Of concern are the emergence of antibiotic-resistant bacteria, resistant forms of parasites, and the lack of vaccines for many of these diseases. These factors have led to a limitation in treatment options, and better prevention strategies are needed.

Some Recommendations

Emerging Hazards

- Coxsackieviruses can exhibit chronic outcomes and these infections should be followed with serology.
- The use of urinary antigen could be used to screen for prevalence for *Legionella* as a cause of indoor respiratory disease.
- All Hanta virus and rodent distributions should be mapped.
- Streptococci skin infections and associated upper respiratory disease should be of interest.

Risk Assessment

- Health surveillance databases need to include asymptomatic infections and quantitative outcomes.
- Dose-response databases should be developed.
- Geographic, climatic, seasonal, dose-response, and exposure scenarios can be used to develop tools for setting priorities for assessment of predeployment risks.
- Risk models can be evaluated for plausibility during outbreak investigations or disease surveillance operations. Exposure and health outcomes must be better assessed.
- The use of quantitative assessments allows one to begin to build exposure scenarios in which thresholds associated with ineffectiveness in the troops in a given time frame can be determined for specific agents.

Biological Weapons

- Dose-response models should be developed.
- Time and concentration exposure and consequence scenarios should be built and evaluated.

Mixtures and Multiple Stressors

- Microbial hazards should be added to animal research studies to test for mixtures effects (e.g., vaccination followed by coxsackieviruses, metals and viruses effects, and nutrition and infection). Special focus should be given to those microorganisms with possible immunological and neurological outcomes.

DOD Infectious Disease Research Laboratories

• One of the major assets in implementing DOD's expand mission on emerging infectious diseases is the overseas research laboratory system that is currently in place. At a minimum, each laboratory staff should be trained in risk-assessment methods, should have PCR capabilities, and be trained in the use of GIS for maintaining and analyzing the databases.

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